DEPARTMENT OF SURGERY

Cancer Control Research Program
Wilmot Cancer Institute

EXERCISE INTERVENTION FOR LESBIAN, GAY, BISEXUAL, AND TRANSGENDER (LGBT) CANCER SURVIVORS

STUDY CHAIR: **Charles Kamen, Ph.D., M.P.H.**

STUDY CO-INVESTIGATORS: Karen Mustian, Ph.D., M.P.H.
Gary R. Morrow, Ph.D., M.S.
Kathi Heffner, Ph.D.
Supriya Mohile, M.D.
Eva Culakova, Ph.D
James McMahon, Ph.D.
Michael Keefer, M.D.
Edward Messing, M.D.
Alexander Solky, M.D.

STUDY MEDICAL MONITOR: Richard Dunne, M.D.

LABORATORY CHAIR: Michelle Janelsins, Ph.D.

STUDY COORDINATOR: Nicole Murray, M.S.

EXERCISE PHYSIOLOGIST: Michelle Porto, Po-Ju Lin, Adam Szczupakowski

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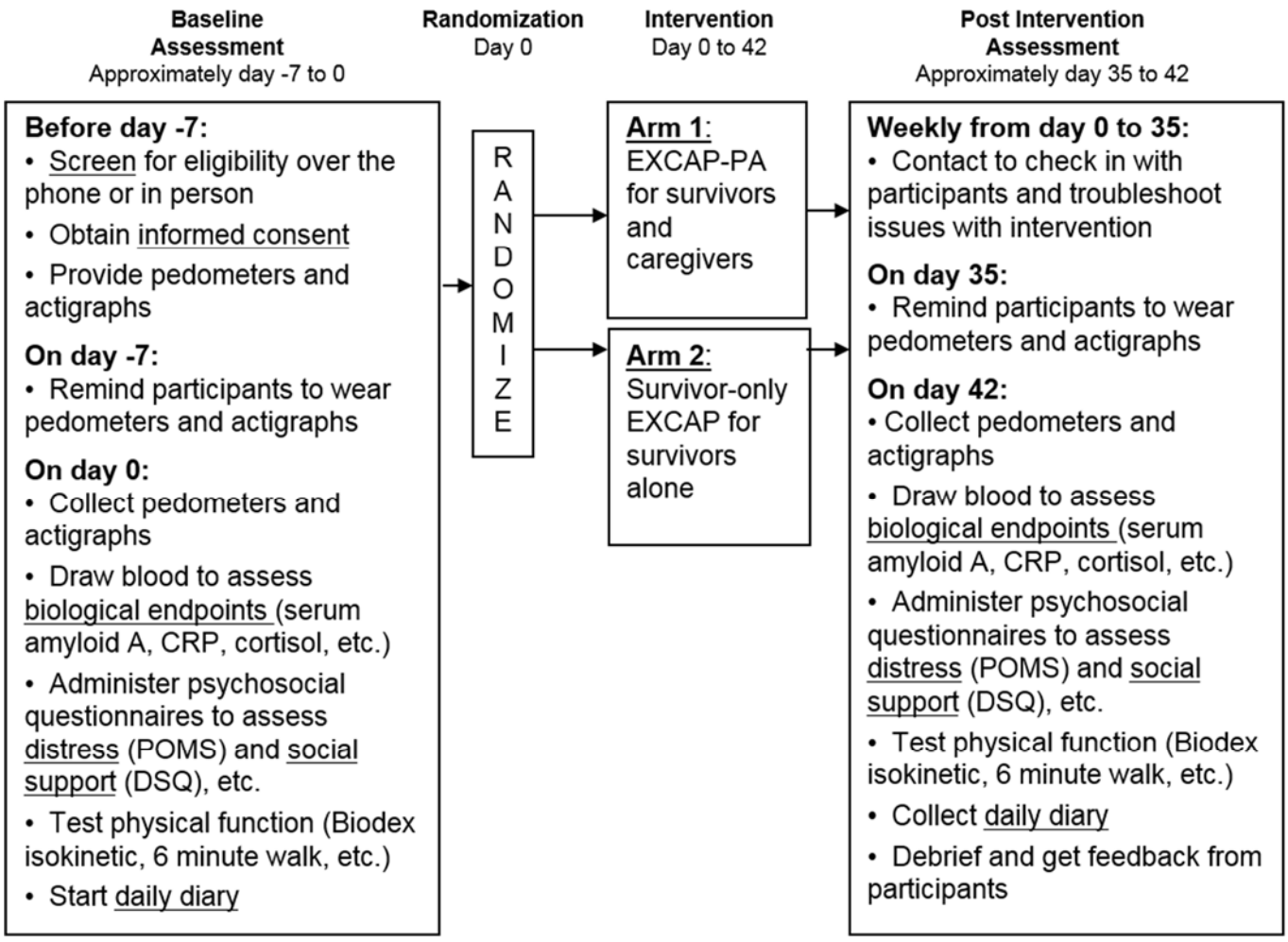
FIGURE 1: Study Schema



POMS=Profile of Mood States, CRP=C reactive protein, DSQ=Dyadic Support Questionnaire

1. STUDY OVERVIEW, PURPOSE, AND BACKGROUND

1.1. Significance of Distress among lesbian, gay, and bisexual (LGBT) cancer survivors

To date, LGBT survivors have been invisible in the cancer control literature.[1,2] Epidemiological studies of cancer prevalence often do not assess sexual orientation,[2] and even studies of the needs of diverse populations of cancer patients and survivors have remained mute on the subject of sexual orientation.[3-5] The few studies that have focused on LGBT cancer issues have found that subgroups of LGBT persons are up to 2.1 times more likely to be diagnosed with cancer than their heterosexual counterparts,[6,7] and that physical and mental health disparities impact LGBT cancer survivors.[7-9] Distress, a negative psychological reaction to the cancer experience, is among the most common side effects cited by survivors of any sexuality,[10,11] is 1.7 times more common among LGBT survivors,[12] and is linked to increased morbidity[13] and mortality.[14] Lesbian survivors report poorer quality of life[8] and more anxiety and depression post-diagnosis than heterosexual women,[9] while gay male survivors report worse mental health and more fear of cancer recurrence than heterosexual men.[15,16] Given the large number of LGBT survivors (between 420,000-1,000,000 living in the United States[17,18]), higher rates of distress among these survivors, and the link between distress, morbidity, and mortality, interventions targeting distress among LGBT cancer survivors are urgently needed. There is also a need for interventions that are socioculturally tailored to the needs of this population.[19,20] Targeting psychological distress in LGBT survivors through a partner-assisted intervention could reduce the public health burden of long-term cancer survivorship by reducing chronic distress and morbidity among survivors[21-23] and promoting intervention adherence.[22-30]

1.2. Exercise as intervention to reduce distress

Receiving a diagnosis of cancer can cause psychological distress.[31] Distress among LGBT cancer survivors is further exacerbated by LGBT-specific stressors, such as discrimination based on sexual orientation and invisibility/non-recognition of caregivers.[1,32] Exercise, including walking and resistance training, is safe and well-tolerated and improves distress in heterosexual cancer survivors.[33-36] Our intervention, EXCAP©® (Exercise for Cancer Patients), is a standardized, daily, 6 week, home-based, progressive exercise program. In phase II randomized controlled trials (RCTs) of this program, survivors (N = 91) who completed EXCAP©® demonstrated improvements in distress, quality of life, and markers of inflammation.[33,37,38] Adherence to the intervention was good (79% completion rate), and there were no adverse events.[33-36] As EXCAP©® is a standardized exercise program, it is easy to prescribe and tailor to survivors; it is home-based, exportable, and may be more palatable than weekly psychotherapy.[39,40]

1.3. Support, distress, and exercise

In our formative research, LGBT survivors reported feeling less distressed when their caregivers were included in cancer care visits.[41] We have also shown that partner support is directly linked to reductions in LGBT-specific stress among LGBT adults.[12,42,43] In tailoring an intervention for LGBT survivors, it is critical to welcome support from caregivers in order to reduce LGBT-specific stress. Also, two RCTs have shown that exercise interventions incorporating support from a caregiver may increase adherence and produce significant improvements in clinical outcomes among cancer survivors.[44,45] In the first, survivors who exercised with a

caregiver were more adherent to the intervention than those who did not.[45] In the second, survivors and caregivers receiving an exercise intervention as a dyad reported less distress.[44] However, neither study compared the efficacy of a partner-assisted exercise intervention to a survivor-only intervention, nor were LGBT survivors recruited. Thus, while preliminary evidence indicates that including caregivers in exercise interventions may be effective, no RCTs have evaluated the efficacy of a partner-assisted exercise intervention in reducing psychological distress among LGBT cancer survivors.[21-23]

1.4 Integrated biopsychosocial model of the impact of exercise on distress: Cancer influences psychological distress on several levels. First, receiving a diagnosis of cancer can produce symptoms of depression and anxiety. [31,46] This distress has been shown to negatively impact both cancer survivors and their caregivers,[2,45-49] reduce the provision of social support within the survivor/caregiver dyad,[10-11] and consequently increase psychological distress. Cancer and treatment also impact stress processes[47] and increase activation of markers of inflammation.[48] Increased activation of the HPA axis and concomitant increases in systemic inflammation can result in increased report of psychological distress.[49-51] In previous studies, cortisol, C-reactive protein, and serum amyloid A are particularly linked to report of distress.[52-57]

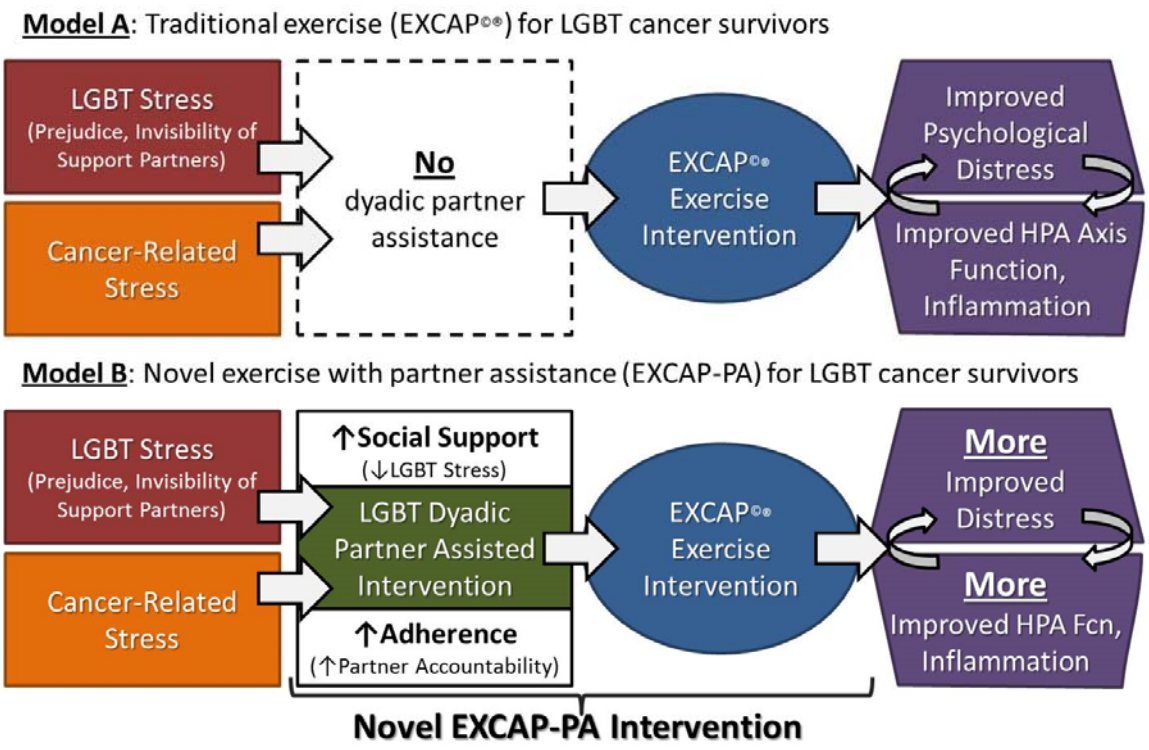


Figure 2: Biopsychosocial model of dyadic intervention

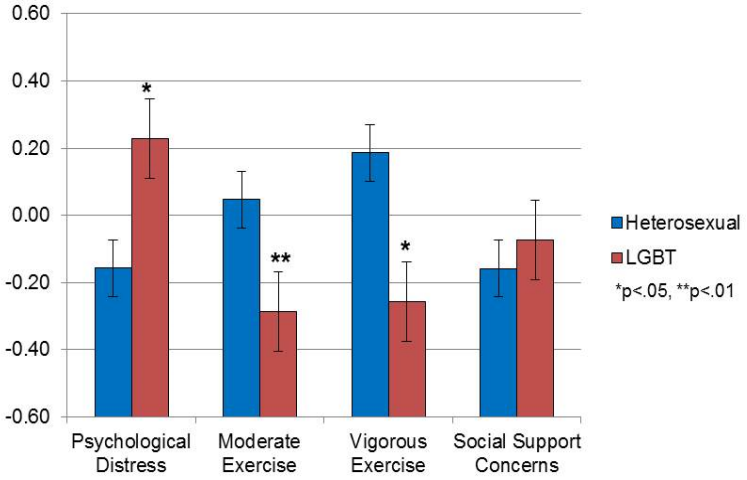
Therefore, EXCAP©® is designed to reduce distress on two levels. On a psychological level, participation in exercise serves as a form of behavioral activation and increases self-efficacy, factors that have been shown to reduce distress.[22-30] On a physiological level, exercise affects biological processes associated with the stress response, as measured by reduction in levels of distress-related biological endpoints (Figure 2).[37] This study will test direct effects of exercise on reduction in psychological distress and these biological endpoints. Previous research on this model by our group has shown that exercise does improve distress and that changes in immune function significantly predict changes in distress ($p<0.05$, $r=0.12$).[38]

Including a caregiver in an exercise intervention, similarly, could affect distress on a psychological level by increasing perception of social support,[58] and on a physiological level by increasing intervention adherence.[45]

1.5 Preliminary data

The preliminary data presented illustrates four key points: 1) Disparities exist among LGBT cancer survivors;

Figure 3: Z-scores comparing LGBT (N=293) and heterosexual (N=5,386) cancer survivors (all cancer types)



2) LGBT survivors and their partners want specific interventions, 3) EXCAP©® is effective in reducing distress, and 4) recruiting and retaining LGBT cancer survivors and caregivers is feasible.

Study 1) Distress is prevalent among LGBT cancer survivors: In secondary data analyses of large datasets (BRFSS, LIVESTRONG), we found that LGBT cancer survivors reported 2.96 more days per month of poor mental health (p=0.02), 60 fewer minutes of physical activity per week (p=0.01), and 1.9 times greater odds of difficulty with social support (p=0.04) than their heterosexual counterparts.[12] (See Figure 3.)

Study 2) LGBT cancer survivors and their partners want specific interventions: In a focus group conducted with 10 lesbian and gay cancer survivors and their caregivers, we (Dr. Kamen, with consultation from mentors) found that **both** cancer survivors **and** their partners experience psychological distress, including concerns about the impact of treatment on their relationship and about cancer recurrence. Multiple dyads reported that this distress directly affected their relationship with one another and that few resources are available for cancer survivors in the LGBT community. **All** LGBT survivors and their caregivers we spoke with indicated that they would be interested in a tailored exercise intervention.

Study 3) The EXCAP intervention is effective in reducing distress: In a secondary analysis of Dr. Mustian's study of EXCAP©® for prostate cancer survivors (n=58), we found that EXCAP©® significantly reduced distress as measured by the POMS Total score. Compared with usual care control, 6 weeks of EXCAP©® was associated with a 7.24 point reduction in the POMS Total score (p = 0.02; manuscript under review).[38] This secondary analysis also included evaluation of immune function; while markers of HPA axis function and early inflammation were not included in this dataset, preliminary analysis of immune function piqued my interest in exploring this biological mechanism further.

Study 4) It is feasible to recruit and retain LGBT cancer survivors and their partners in an exercise intervention: Dr. Kamen was recently (2013) awarded a seed grant to conduct a feasibility study, entitled "Dyadic Exercise Intervention for Heterosexual and LGBT Cancer Survivors and Their Caregivers." This study, conducted with the input of the mentorship team, was designed to assess the **feasibility and acceptability** of delivering an exercise intervention to heterosexual and LGBT dyads, as well as establishing **preliminary efficacy of the same outcome measures to be used in the proposed Phase II RCT.** We developed a novel, dyadic delivery method for EXCAP©® (EXCAP-PA; see Appendix), involving training caregivers to support survivors in exercising, as well as new LGBT recruitment and retention methodologies. We have recruited and retained 20 LGBT survivors and their diverse caregivers, successfully delivered the intervention, and had good adherence and acceptance. We also built strong community collaborations and partnerships.

2. HYPOTHESIS AND AIMS

2.1. Overall Hypothesis

The overall hypothesis of this study is that among LGBT survivors, EXCAP-PA, incorporating caregiver support, will be more efficacious than survivor-only EXCAP©® in improving biopsychosocial aspects of distress: both self-reported psychological distress and biological endpoints associated with distress. Exploratory hypotheses are that improvement in distress, increased social support from the caregiver, and intervention adherence will be positively related, and that caregivers will also benefit from partner-assisted intervention.

2.2 Primary Aim (in survivors)

2.2.1 To determine the preliminary effect of EXCAP-PA versus survivor-only EXCAP©® on self-reported psychological distress (Profile of Mood States [POMS] total score).

2.3 Secondary Aims (in survivors)

2.3.1 To determine the preliminary effect of EXCAP-PA versus survivor-only EXCAP©® on biological endpoints associated with distress: markers of HPA axis functioning (cortisol) and markers of early inflammation (serum amyloid A [SAA], C-reactive protein [CRP])

2.3.2. To determine the preliminary effect of EXCAP-PA versus survivor-only EXCAP©® on social support from the caregiver (Dyadic Support Questionnaire [DSQ]) and intervention adherence (actigraphy).

2.4 Exploratory Aims (in survivors):

2.4.1 To explore preliminary mechanistic relationships between self-reported distress, markers of HPA axis functioning and early inflammation, social support from the caregiver, and intervention adherence.

2.5 Exploratory Aims (in caregivers):

2.5.1 To determine the preliminary effect of EXCAP-PA versus survivor-only EXCAP©® on self-reported psychological distress and biological endpoints associated with distress among caregivers.

3. CHARACTERISTICS OF THE RESEARCH POPULATION

Targeted/Planned Enrollment Table

Total Planned Enrollment: 140

TARGETED/PLANNED ENROLLMENT: Number of Participants			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	7	7	14
Not Hispanic or Latino	63	63	126
Ethnic Category: Total of All Participants	70	70	140
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	2	2	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	10	10	20
White	58	58	116
Racial Categories: Total of All Participants	70	70	140

3.1 **Subject Characteristics and Number of Participants**

Participants in this randomized controlled trial will be 70 LGBT cancer survivors and their 70 caregivers (a total of 70 dyads/140 individuals). A caregiver is defined as any individual whom the cancer survivor nominates as having provided emotional support or tangible assistance without pay during the survivor's cancer experience. No restriction will be placed on caregivers in terms of relationship with the cancer survivor; they can be family members, friends, romantic partners, or community members.

3.2 **Gender, Age, and Racial/Ethnic Origin of Participants**

Based on the characteristics of samples recruited for previous exercise studies run out of the **P**hysical **E**xercise **A**ctivity **K**inesiology Laboratory (**PEAK** Lab) at the University of Rochester, we anticipate that the sample for the current study will be 49% male and 51% female. Average age will be 67 years. The ethnic composition of the sample will be approximately 92% White/Caucasian, 15% African-American, and 3% Asian; 10% will

report a Hispanic/Latino ethnicity. Children, as defined by the National Institutes of Health Grants Policy Statement, will not be included, as cancer survivors under 21 years of age are often considered to fall under pediatric care, and may have a very different experience of cancer and caregiving than adult (age 21+) cancer survivors.

3.3 **Inclusion Criteria (Survivors):** To be included in the study, cancer survivors must:

3.3.1 Have had a diagnosis of cancer (any cancer type excluding squamous and basal cell [skin cancers]) and have completed primary surgery, chemotherapy, and/or radiation therapy (those on continued, indefinite adjuvant treatment are still eligible),

3.3.2 Identify as lesbian, gay, bisexual, or transgender, or have a same-sex romantic partner,

3.3.3 Have a caregiver willing to participate in the study (defined as anyone who provided emotional support or tangible assistance during the survivors' cancer experience),

3.3.4 Be able to read English,

3.3.5 Be 21 years of age or older, and

3.3.6 Give written informed consent or electronic consent.

3.4 **Inclusion Criteria (Caregivers):** Caregivers must:

3.4.4 Be nominated by a cancer survivor,

3.4.5 Be able to read English,

3.4.6 Be 21 years of age or older,

3.4.7 Give written informed consent or electronic consent.

3.5 **Exclusion Criteria:** Participants must not:

3.5.4 Have physical limitations (e.g., cardiorespiratory, orthopedic) contraindicating participating in a low- to moderate-intensity home-based walking and progressive resistance program and physical function testing, as assessed by their medical oncologist, their primary care physician, and/or the study medical monitor (or any of these three physicians' designees),

3.5.5 For caregivers, be currently undergoing active treatment for cancer.

4. PARTICIPANT IDENTIFICATION, RECRUITMENT AND CONSENT

4.1 Human Subjects Involvement: The proposed RCT aims to recruit 70 lesbian, gay, bisexual, and transgender (LGBT) cancer survivors who have completed treatment (surgery, radiation, or chemotherapy) or who are on continued, indefinite adjuvant treatment, so as to have a final, evaluable sample of 60 LGBT survivors after attrition. The proposed RCT will also recruit caregivers (broadly defined) of the above cancer survivors. Each recruited cancer survivor will be asked to name a person who they feel provided care (emotional, informational, tangible, etc.) during their cancer experience, with no further strictures placed on this relationship in terms of type or duration. The caregiver will be approached to participate in the RCT. Thus the sample will consist of 70 LGBT survivors (60 evaluable) and their caregivers (140 individuals total/120 evaluable). Recruitment and primary analyses will specifically target the LGBT cancer survivor.

LGBT survivors will be randomized to one of 2 arms: Arm 1, a novel, *partner-assisted*, LGBT-specific framework incorporating EXCAP©® (Exercise for Cancer Patients, a standardized, daily, 6 week, progressive walking and resistance training program), in which both survivors and caregivers will receive EXCAP©® materials and be instructed in their use together, or Arm 2, a *survivor-only* version of EXCAP©®, in which only the cancer survivor will receive EXCAP©® materials and be instructed in their use. There will be 35 LGBT survivors randomized to each arm (30 evaluable), along with their 35 caregivers (30 evaluable). Survivors and caregivers will be assessed before and after the 6 week intervention in both arms. The LGBT survivor will be the primary unit of analysis; data collected from caregivers will be used for exploratory purposes only.

Assuming an 85% retention rate and an initial sample of 70 survivors, 60 LGBT survivors will complete the study. Because LGBT survivors are the primary unit of analysis, survivors will be invited to return for follow-up assessment even if their caregivers are unavailable. Study interventions will begin on Study Day 0 and continue for 6 weeks (42 days). The exercise intervention, EXCAP©®, is a standardized intervention developed and tested by the research team at University of Rochester Medical Center (URMC). The actual list of exercises, and the framework for the partner-assisted EXCAP-PA, is provided in the Appendix. Each participant will be monitored by an American College of Sports Medicine Certified Exercise Physiologist℠. Assessments will be made with validated and methodologically sound measures including self-report questionnaires, assays for expression of biological endpoints, weekly diaries, and actigraphy monitoring.

No special classes of participants such as fetuses, neonates, pregnant women, prisoners, institutionalized individuals or other vulnerable populations will be recruited.

Children, as defined by the National Institutes of Health Grants Policy Statement, will not be included, as cancer survivors under 21 years of age are often considered to fall under pediatric care and may have a very different experience of cancer treatment and caregiving than adult (age 21+) cancer survivors.

All data will be gathered at the PEAK Lab and the URMC Cancer Control Unit.

4.2 Method of Participant Identification and Recruitment

4.2.1 LGBT Survivor Recruitment: All data will be gathered from participants 21 years of age or older. Participants are cancer survivors who have completed treatments or caregivers of cancer survivors; both survivors and caregivers are able to read and understand English. Potentially eligible cancer survivors will be contacted through several channels.

1) Distal identification of URMC patients: First, the study team will monitor URMC patients over the age of 21 who have been diagnosed with cancer (any site), who have completed cancer treatment or are on indefinite treatment, and who are LGBT identified or same-sex partnered. This monitoring will be done through e-record as well as with TriNetX, a clinical query tool that allows researchers to pull specific subject criteria from e-record. Search criteria for TriNetX will include "malignant neoplasm" as well as other specific cancer diagnoses, report of being "partnered" or having a "same-sex partner" on sociodemographic questions, or identifying as lesbian, gay, bisexual, or transgender. Use of TriNetX software requires an RSRB approved protocol; any data from this service is transferred to the study team via a secure web-based interface. If an LGBT cancer survivor identified via TriNetX is deemed eligible after a review of their medical record, the study team will contact the survivors' physician to ensure eligibility and will then send the survivor a letter, from their physician and the study team, explaining the study and its requirements. A brochure providing further details will also be enclosed (see Recruitment Materials). Survivors will have the option to opt out of further contact; if the survivor is willing to continue, a study team member will make contact to conduct screening.

2) Direct referral of URMC patients: Second, study staff work with physicians, nurses, and other care providers in URMC clinics to identify patients who have been diagnosed with cancer (any site), who have completed cancer treatment or are on indefinite treatment, and who have identified themselves as LGBT or same-sex partnered to their care providers. After being referred by their care provider and deemed eligible following a review of their medical record, survivors will be sent a letter from their physician and the study team, explaining the study and its requirements. Study team members will also be present in the URMC clinics of affiliated care providers so that cancer survivors who are scheduled for appointments and who might be eligible can be referred by their treatment team to the study. Following the referral by the treatment team, the treatment team will introduce the study team member, who will meet with the survivor and explain the study either in person or over the phone. If a caregiver has accompanied the survivor to the clinic, they will be informed about the study at the same time, either in person or via phone. If the survivor (and caregiver) is willing to continue, a study team member will conduct screening. Letters and brochures describing the study will be sent to the homes of survivors and caregivers contacted at the clinic.

3) Community recruitment and referral: We will also advertise the study on the University of Rochester Medical Center "Clinical Trials" website, in local newspapers, through flyers posted in the community, and through the PEAK Lab Facebook page. To ensure recruitment of LGBT cancer survivors, we will also recruit through community groups, such as those hosted by the Out Alliance of the Genesee Valley and through providers at Trillium Health, who specifically provide services to the LGBT community; we will leave brochures and tear-off posters at both locations and present the study to staff at both locations. We will recruit through newspaper

advertisements; through website postings targeting the LGBT community; and through word-of-mouth, referrals, and snowball recruitment within the LGBT community.

Snowball recruitment methods will involve asking recruited participants to pass information about the study on to other interested LGBT cancer survivors and/or their caregivers. Due to the stigmatized nature of LGBT identities and cancer diagnoses, steps will be taken to ensure that recruited participants do not feel unduly coerced to participate in snowball recruitment and that the confidentiality of other LGBT cancer survivors in the community is maintained. We will include verbiage in the consent form whereby recruited participants can indicate whether they are willing to contact other LGBT community members about the study. Those who consent to contact other LGBT community members will be provided with RSRB approved brochures to give to potentially eligible community members. Research staff will follow up with these participants while study recruitment is ongoing to see if they need additional brochures; if so, additional brochures will be mailed to participants' home addresses.

Interested potential participants who contact the study through any of these means will be mailed a letter and brochure and screened via phone by a member of the study team.

4.2.2 Caregiver Recruitment: A similar procedure will be followed for the caregiver; after being nominated by a survivor, the caregiver will be told about the study immediately (if the caregiver is present at a clinic visit or with the cancer survivor during telephone contact), or sent a letter from the study team explaining the study and providing the option to opt out of future contact. If the caregiver is willing to continue, the study team member will conduct screening.

4.3 Screening: After a member of the treatment team has referred the potential participant, or the potential participant has contacted the research team, screening of potential study participants will be conducted either in person or over the phone by research staff trained to explain the project, recruit, and screen participants (see Telephone Script). Verbal consent to conduct this screening will be obtained using the telephone script. Screening will focus on the cancer survivor's eligibility, with caregivers nominated by survivors. Individually identifiable information will not be kept on potential participants who decline to participate in the study, though we will note gender and race/ethnicity for the purpose of monitoring our success in recruiting women and racial/ethnic minorities.

Eligibility of the dyad will primarily be established using cancer survivors' characteristics. After a member of the treatment team has referred the LGBT cancer survivor or the survivor has contacted the research team, the survivor will be screened for eligibility either via telephone or face to face. In both screening approaches, a trained staff member will ask survivors about: (1) cancer diagnosis and treatment, (2) identification as lesbian, gay, bisexual, or transgender, or partnership with a same-sex romantic partner, (3) medical contraindications to exercise, and (4) presence and availability of a primary caregiver.

Following screening of the cancer survivor, a study team member will ask for the survivor to nominate a caregiver. Caregivers will then be screened either via telephone or face-to-face. After the caregiver has been contacted by the study team for screening, or if the caregiver initiates contact with the study team, screening

will focus on assessing willingness to participate and ruling out medical contraindications to engaging in moderate walking and resistance training.

After completing screening of survivors and caregivers, a study team member will schedule survivors and caregivers for an informed consent session at the PEAK Lab, or will offer the option for participants to complete an electronic consent form (e-consent). If consent is obtained in person, caregivers and survivors can attend this session either as a dyad or as individuals; if consent is obtained electronically, caregivers and survivors will be sent individual copies of the e-consent form (see section 4.4 below).

After screening and establishing informed consent, but before the baseline assessment, medical eligibility for participants will be further verified by contacting the survivor's and caregiver's oncologist or primary care physician. With the participants' verbal consent, a study team member will fax a form indicating that the participant has no medical contraindications to participating in a moderate intensity exercise program or physical function assessment (see Appendix). The physician (or designee) will verify and sign this form. The form will be returned to the study team before the baseline assessment meeting. Alternately, the medical monitor will assess the participant to rule out medical contraindications to participating in a moderate intensity exercise program.

After consenting and verification that there are no medical contraindications to participating in an exercise program or physical assessment for either participant, dyads will be scheduled to return to the PEAK Lab for a baseline assessment and randomization to an intervention arm.

4.4 Consent Process

4.4.1 **In-person consent:** To ensure appropriate safety precautions when conducting in-person study procedures, the process for conducting in-person visits outlined in the Guidance for Human Subject Research will be followed. After recruitment and screening, a time is scheduled for survivor and caregiver to come to the PEAK Lab to complete the consent form, either separately or together. If they arrive together, the study team member walks each individual through the consent form to ensure comprehension. Survivors and caregivers are given the option to sign the consent form. The study team member is available to answer any questions the survivor or caregiver may have about any aspect of the study prior to consenting and throughout the entire study period.

4.4.2 **Electronic consent:** In lieu of the paper-based consent document, consent may occur remotely using the RSRB-approved eConsent document provided via REDCap. The study staff will screen for potential participants using the above screening procedures and initiate initial contact via phone, briefly describing the study and asking them to contact us if they would like more information. If a potential participant is interested, the study team will talk to the person on the phone and obtain verbal permission from the participant to send an email or text message stating, "Because URMC can't control the security of email or text messages once we send them, we need your permission to text or email you. Do you want to receive a copy of the consent document and a link to the eConsent via text or email?" Written permission from the patient will be documented. We will then email or text a pdf version of the eConsent document for the

participant to read. We will then set up a phone call or Zoom meeting (participant's choice) to formally go over the consent document. During this phone or Zoom meeting, we will provide a link to the REDCap eConsent document as well as instructions on how to access the eConsent—we will use verification with a passcode based on known information (e.g., the patient's home zip code). No personal health information will be sent via any emails/texts. The eConsent documents may be viewed on computers, electronic tablets, or smartphones. The pdf copy of the eConsent and the REDCap eConsent will have identical information; it will be optional for the person to review the consent before the study team discusses it with them. After a member of the study team reviews the consent document with the participant over the phone or computer, they will have the opportunity to electronically sign the eConsent via REDCap. Signatures will be obtained by asking participants to type in their name. The person obtaining consent will then add their name and a timestamp to the study participant's signed eConsent form in REDCap. In order to authenticate the identity of the participant signing the eConsent, we will again ask the participant to use a passcode based on known information (e.g., the participant's year of birth) for verification. Once the eConsent form is signed and submitted, the patient and/or legally authorized representative will be able to print a paper copy, download a pdf, and/or receive an email with a PDF attachment of the signed consent form. A similar process will also occur with the identified caregiver.

4.4.3 After providing written or electronic informed consent, the survivor and caregiver, with the help of the study team member, will complete a Physical Activity Readiness Questionnaire (PAR-Q+), an On-Study Data Form, a Clinical Record Form and a Medication Form providing demographic and clinical data. The study team member will obtain information necessary to complete these three forms from the survivor's electronic medical records when the survivor is unable to provide this information in sufficient detail (e.g., staging, surgical procedures, types and doses of treatments). Information from the caregiver's physician will be used to complete these three forms when the caregiver is unable to provide information in sufficient detail.

4.4.4 The study chair, study coordinator, and Certified Exercise Physiologist^{SM} have received appropriate training, as well as password secured access to use the University of Rochester Medical Center's electronic patient scheduling and clinical information systems to obtain medical information and appropriate source documentation for research files.

5. RANDOMIZATION

Survivors and their caregivers who meet the eligibility criteria, sign the informed consent form and complete all baseline assessments will immediately be randomized as a dyad to one of two trial arms by means of a computer-generated randomization table.

5.1 A total enrollment of 70 cancer survivors and their 70 primary caregivers is planned (70 dyads total, 35 dyads per trial arm).

5.2 The two trial arms will be as follows:

Trial Arm	Condition
1	*Dyadic Exercise Intervention (EXCAP-PA):* Progressive walking and resistance exercise treatment, prescribed to both cancer survivors and their caregivers (daily walking and up to 7 times/week resistance prescription for 6 weeks). Cancer survivor and caregiver are also asked to discuss ways they can support one another in a) remaining adherent to exercise, and b) dealing with stress, including LGBT-specific minority stress.
2	*Individual Exercise Intervention (EXCAP):* Progressive walking and resistance exercise treatment, prescribed solely to cancer survivors (daily walking and up to 7 times/week resistance prescription for 6 weeks). The caregiver is told not to change his/her exercise behavior in any way.

6. METHODS AND STUDY PROCEDURES

6.1 ***Objective****:* This will be a two-arm randomized controlled trial examining the efficacy of a dyadic, partner-assisted home-based walking and progressive resistance exercise program (EXCAP-PA) vs. an individual, survivor-only home-based walking and progressive resistance exercise program (EXCAP) for the relief of psychological distress among LGBT cancer survivors. This is an ancillary cancer control intervention, administered for control of psychological symptoms caused by LGBT minority stress, caregiver stress, cancer, and/or cancer treatment.

6.2 ***Recruitment and Screening****:* The study team will recruit and screen survivors prior to scheduling an initial visit to establish informed consent via several mechanisms, listed below.

6.2.1 LGBT or same-sex partnered cancer survivors (any cancer type except squamous or basal cell skin cancers), finished with treatment or on indefinite treatment, along with a caregiver (broadly defined and designated by the survivor), will be invited to participate in the study.

6.2.2 Potentially eligible LGBT cancer survivors will be contacted through several channels:

6.2.2.1 By a letter from the study team and physician, after being identified and screened for eligibility through e-record or i2b2

6.2.2.2 Directly by a member of the study team, after being introduced by a physician or care team member at a URMC clinic

6.2.2.3 Through the University of Rochester Medical Center "Clinical Trials" website

6.2.2.4 Through advertisements posted in local newspapers (the Empty Closet, etc.)

6.2.2.5 Through flyers posted in locations in the community (coffee shops, etc.)

6.2.2.6 Through the PEAK Lab Facebook page

6.2.2.7 Through brochures and tear-off posters left at local organizations serving the LGBT community (the Out Alliance of the Genesee Valley, Trillium Health, etc.)

6.2.2.8 Through advertisements posted on websites frequented by members of the LGBT community (Craigslist Men Seeking Men and Women Seeking Women, etc.)

6.2.2.9 Through word-of-mouth (snowball recruitment)

6.2.3 The study team monitors URMC patients who may be eligible to participate via e-record and i2b2. They also work with physicians and care team members, including co-investigators Drs. Mohile, Tejani, Keefer, Messing, Solky and Dunne, to identify LGBT cancer survivors who may be eligible for this study. A member of the study team contacts the physician, their designee, or another care team member and lets them know that a survivor may be eligible for the study; alternately, the physician, their designee, or a care team member may recommend a survivor as a good study candidate.

6.2.3.1 After identifying a potentially eligible participant, the physician or care team member introduces the study and a member of the study team to the survivor during a scheduled

clinic visit. The member of the study team describes the study. If the survivor is willing to continue, the study team member conducts screening. The physician or care team member (or their designee) then signs a form that states the survivor has no medical contraindications to participating in the study.

6.2.3.2 Alternately, a letter from the study team and physician is sent to the survivor's home, explaining the study. If the survivor is willing to continue, the study team member conducts screening. The physician or care team member then signs a form that states the survivor has no medical contraindications to participating in the study.

6.2.4 A similar procedure will be followed for the caregiver; after being nominated by a survivor, the caregiver will be sent a letter from the study team, explaining the study. If the caregiver is willing to continue, the caregiver will be screened for eligibility. To establish medical eligibility, the caregiver's primary care physician (or designee) will verify and sign a form, created by the study team, indicating that the caregiver has no medical contraindications to participating in the study. Alternately, the medical monitor will assess for medical contraindications.

6.2.5 If the survivor or caregiver has made contact with the study team after hearing about the study through a community-based recruitment channel, or if a study team member has already made contact with the survivor or caregiver in person following referral by the survivor's treatment team, the study team member continues by explaining the details of the study. In talking to the survivor, the study team member screens for eligibility and confirms whether or not the survivor has a primary caregiver who may also be eligible to participate in the study. In talking to the caregiver, the study team member screens for eligibility. During this discussion, the study team member uses the informed consent document as a guide, goes over details of the study with potential participants either in person or on the phone, and recruits them to the study.

6.3 ***Consent process and pre-baseline assessment***

6.3.1 Following recruitment and screening, a time is scheduled for survivor and caregiver to come to the PEAK Lab to complete the consent form, either separately or together. If they arrive together, the study team member walks each individual through the consent form to ensure comprehension. Survivors and caregivers are given the option to sign the consent form. The study team member is available to answer any questions the survivor or caregiver may have about any aspect of the study prior to consenting and throughout the entire study period.

6.3.2 If participants prefer to consent to the study remotely, an electronic consent will be provided to them; procedures for this were explained in section 4.4.2.

6.3.2 After providing written or electronic informed consent, survivor and caregiver, with the help of the study team member, will complete a Physical Activity Readiness Questionnaire (PAR-Q+), an On-Study Data Form, a Clinical Record Form and a Medication Form providing demographic and clinical data. The study team member will obtain information necessary to complete these forms from the survivor's electronic medical records when the survivor is unable to provide this information in sufficient detail (e.g., staging, surgical procedures, types and doses of treatments).

Information from the caregiver's physician will be used to complete these three forms when the caregiver is unable to provide information in sufficient detail.

The study chair, study coordinator, and Certified Exercise Physiologist[SM] have received appropriate training, as well as password secured access to use the University of Rochester Medical Center's electronic patient scheduling and clinical information systems to obtain medical information and appropriate source documentation for research files.

6.3.3 During the consent meeting, all participants will be given a pedometer (or a fitness tracker such as the FitBit) and an Actigraph to wear for approximately 4-7 consecutive days before the baseline assessment. The pedometer (or fitness tracker) and actigraph will be collected at the baseline assessment and returned to all participants for approximately 4-7 days of monitoring prior to the post-intervention assessment.

6.3.4 The study team member will schedule a time for survivor and caregiver to return to the PEAK Lab to complete the baseline assessment. The study team member will make phone or e-mail contact with survivor and caregiver approximately 7 days before their scheduled baseline assessment to remind them to wear their pedometers (or fitness trackers) and actigraphs.

6.4 ***Baseline assessment***

6.4.1 **All assessments will be done on all study participants (cancer survivors and their caregivers).** Survivors and caregivers can complete assessments either as a dyad or individually. The sequence of assessments will be the same at baseline and post-intervention.

6.4.2 **Blood draw.** At the baseline assessment (and again at the post-intervention assessment), blood sampling will be done to estimate hematocrit, hemoglobin, lymphocytes, monocytes, and biological endpoints of interest (serum amyloid A, CRP, cortisol, along with mRNA concentrations of these endpoints). Blood draws can be conducted with cancer survivor and caregiver together or separately, on the same day as the baseline assessment or up to a week before the baseline assessment. The consent form will include a section asking whether participants agree to have their samples biobanked for additional, future analyses. Participants will have the option to check yes or no to having their samples biobanked.

6.4.2.1 All blood draws will occur in the General Clinical Research Center (GCRC). Survivors and caregivers will report for the blood draw fasted (for a minimum of 8 hours) on the day of the scheduled blood draws. The blood will be drawn by licensed phlebotomists and participants will be offered breakfast/a snack after the blood draw. The time of day will be noted, with future assessments at approximately the same time of day during post-testing. (Note. A total of two blood samples will be taken: one at baseline and one post-intervention. These time points are relevant to assess the influence of the activity intervention on biological endpoints, as well as the association between these biological endpoints and distress at follow-up.) If a cancer survivor is having blood drawn by a licensed phlebotomist as part of a clinical procedure and prefers to have blood drawn for

this study at the same time, rather than at the GCRC, we will work with the survivor and phlebotomist to arrange for the blood draw to occur per protocol.

6.4.2.2 A total of approximately 34 ml of blood (around 2 tablespoons) will be drawn at each time point (baseline and post-intervention assessment). The blood draws for estimation of biological endpoint levels will use 2 red top tubes for serum (10 ml each, 20 ml total). These tubes will be inverted 3-4 times, allowed to clot for 30 minutes at room temperature, centrifuged for 10 min at 1500 x g and then frozen at -20c or -80c. The blood draw for estimation of biomarker genomics will use 1 purple top EDTA-heparin tube (10ml total). This EDTA tube will be rocked 10 times, stored upright for minimum of 2 hours at room temperature and then frozen at -20c or -80c. All tubes will be collected by a study team member and transferred to a secured -80c freezer in lab space maintained by Dr. Janelsins in the Department of Surgery.

6.4.2.3 Blood counts will be obtained either through the medical record (for survivors) or by drawing blood into 1 purple top EDTA-heparin tube (approximately 4ml) and conducting standard CBC with differential procedures (for caregivers and for survivors when blood counts are not available in the medical record).

6.4.3 **Breakfast/snack and sequence of assessments**. After having blood drawn, all participants will be offered breakfast/a snack in the PEAK Lab. If participants arrive together as a dyad, the cancer survivor will begin completing questionnaires while the caregiver completes physical function assessments. If the survivor and caregiver arrive separately, the survivor will complete questionnaires first, followed by physical function assessment, while the caregiver will complete physical function assessments first, and followed by questionnaires.

6.4.4 **Questionnaires.** Psychosocial, survey-style questionnaire assessments will be conducted at baseline and post-intervention, will take less than 1 hour, will consist primarily of quantitative (closed-ended) questions, and will employ the REDCap online survey system, licensed to the University of Rochester. The REDCap questionnaires will be coded by a member of the study team who has experience coding and creating questionnaires and with the methodology of REDCap questionnaire entry. REDCap questionnaires will also be extensively tested prior to recruitment of participants. The quality of psychological and behavioral data is enhanced through use of REDCap because data entry errors due to skip patterns are removed. All participants are given an ID code that will be used when the final dataset is de-identified. This de-identified dataset will be downloaded from the REDCap server space onto a password protected server. REDCap uses encryption algorithms to protect participant data.

All survivors and caregivers will be given a demographics and treatment measure, as well as measures of mood (Profile of Mood States, **POMS**), depression (Patient Health Questionnaire-9, **PHQ-9**), anxiety (State/Trait Anxiety Inventory, **STAI**), quality of life (Short Form Health Survey 12, **SF-12**), support from their study partner (Dyadic Adjustment Scale-7, **DAS-7**; Dyadic Support Questionnaire, **DSQ**; Social Provisions Scale, **SPS**), patient-reported health (**PROMIS** item banks), minority stress (Heterosexism and Identity Questionnaire), sleep and fatigue (Insomnia

Severity Index, **ISI**; Multidimensional Fatigue Symptom Inventory, **MFSI**), interaction with their physician **(**Personal Efficacy in Physician-Patient Interaction, **PEPPI;** the Human Connection, **THC**; Stanford Self-Efficacy, **SSE)** and physical activity (Aerobics Center Longitudinal Physical Activity Questionnaire, **ACLS**) to complete.

6.4.5 **Physical function assessments.** Additionally, participants will be evaluated on **1)** body composition (bioelectrical impedance), **2)** heart rate variability, **3)** muscular strength (Handgrip Dynamometry, isokinetic knee flexion/ extension and shoulder diagonal), and **4)** aerobic capacity (6 minute walk test), in that order. All physiological fitness testing will be administered according to the Guidelines for Exercise Testing and Prescription (GETP) as outlined by the American College of Sports Medicine (ACSM). (See section 10.2 for additional details.)

6.4.6 Data from pedometers (or fitness trackers) and actigraphs will also be collected for analysis. Data from pedometers will be used to inform the walking prescription of the exercise interventions.

6.4.7 **Randomization.** Following completion of physical functioning assessments, dyads will be randomized to a trial arm. Instructions and an exercise kit for the home-based walking and progressive resistance exercise program will be given to survivors and caregivers together in Arm 1 and cancer survivors alone in Arm 2. Caregivers in Arm 2 will receive instructions and an exercise kit following the post-intervention assessment.

6.4.7.2 Cancer survivors and caregivers in dyads randomized to Arm 1 (EXCAP-PA) will each receive a home-based walking and progressive resistance exercise program to follow for a total duration of approximately 6 weeks. These dyads will be instructed in ways to use the exercise kits together. They will also meet briefly with a member of the study team, who will guide them through a discussion of barriers to exercise, ways they can support one another in remaining adherent to exercise, and ways of dealing with stress (including LGBT minority stress).

6.4.7.1 Cancer survivors in dyads randomized to Arm 2 (survivor-only EXCAP) will receive a home-based walking and progressive resistance exercise regimen to follow for a total duration of approximately 6 weeks. Caregivers in dyads randomized to Arm 2 will be told not to change their exercise behavior in any way, will not receive an exercise regimen to follow during the study period and will not discuss dyadic support with the cancer survivor.

6.5 ***EXCAP:*** Home-Based Walking and Progressive Resistance Exercise Program

6.5.1 The Home-Based Walking and Progressive Resistance Exercise Program is designed by an Exercise Scientist certified by the American College of Sports Medicine (ACSM) and is in accordance with the guidelines for exercise testing and prescription as set forth by the ACSM.

6.5.2 The Home-Based Walking and Progressive Resistance Exercise Program will follow the guidelines listed below.

6.5.2.1 The Home-Based Walking Prescription will be based on a participant's (i.e., survivor's or caregiver's) baseline pedometer assessment. Participants will be given a pedometer (or fitness tracker) and encouraged to increase their total steps walked by a minimum of 5% a week during the 6-week intervention while maintaining a moderate intensity. [Note: Walking intensity will be monitored via the Rating of Perceived Exertion (RPE) Scale, which is a visual analog scale ranging from 1 = no exertion at all to 10 = very strong exertion. Participants will be instructed to aim for an RPE of 5-8, consistent with other studies of EXCAP for cancer survivors.] The upper threshold of the walking prescription of the EXCAP program will be 12,000 steps per day.

6.5.2.2 The Home-Based Progressive Resistance Prescription will be based on a participant's baseline isokinetic strength assessment. Participants will be instructed on the proper use of resistance bands. Participants will then be instructed to choose a resistance band with which they can perform 8-12 repetitions of 5 upper body resistance exercises (bicep curl, tricep extension , chest press, rows, and overhead press) and 5 lower body resistance exercises (leg curl, leg extension, squat, toe raises, and side bends), plus core strengthening exercises. Participants will be instructed to begin with 1 set of 8-12 repetitions at a moderate to challenging level (RPE 5-8), up to 7 times per week. Participants will be instructed to progressively increase to 4 sets for each exercise 3 times per week. (Note. Survivors and caregivers in Arm 1 will both be instructed in the proper methods for performing each exercise as a dyad. Cancer survivors in Arm 2 will be instructed in the proper methods for performing each exercise individually.)

6.5.2.3 Participants will be instructed in the proper methods for performing each exercise by an ACSM Certified Exercise Physiologist^{SM}. For those randomized to the dyadic intervention, this will involve a 45-60 minute meeting between the Physiologist and both the survivor and the caregiver. For those randomized to the individual intervention, this will involve a 45-60 minute meeting between the Physiologist and the survivor alone.

6.6 ***EXCAP-PA:*** Partner-Assisted Home-Based Walking and Progressive Resistance Exercise Program

6.6.1 Those randomized to Arm 1, the Partner-Assisted version of EXCAP, will receive the EXCAP program instruction as a dyad, as described above. After the Physiologist has demonstrated proper methods for performing each exercise to the dyad, a trained member of the study team will meet with participants. This meeting will involve a discussion of barriers that might reduce adherence to the intervention for each participant, ways that cancer survivor and caregiver can support one another in remaining adherent, and ways of dealing with stress (including LGBT minority stress). Those randomized to Arm 2, survivor-only EXCAP, will not discuss dyadic support or ways of dealing with stress.

6.7 ***Intervention contact and tracking***

6.7.1 A study team member will make phone or e-mail contact with participants each week to answer any questions they may have regarding the exercise program and to facilitate proper adherence

and compliance to the exercise intervention. In Arm 1, the team member will speak with both the cancer survivor and the caregiver together. In Arm 2, the study team member will speak with the cancer survivor alone.

6.7.2 Participants will also complete a daily diary throughout the intervention period recording mood/psychological distress (all study participants) and physical activity (those randomized to receive exercise only). (Note: The daily diary will take approximately 30 seconds to complete.)

6.7.3 All Walking and Progressive Resistance Exercises will be performed off-site from the University of Rochester Cancer Center in a home-based participant-selected environment.

6.8 ***Post-intervention assessment***

6.8.1 Procedures for the post-intervention assessment will follow those from the baseline assessment. First, blood sampling will be done to estimate hematocrit, hemoglobin, t-cells and biological endpoints (e.g., serum amyloid A, CRP, cortisol). Again, a total of approximately 34 ml of blood (around 2 tablespoons) will be drawn, as was done in the baseline assessment.

6.8.2 After having blood drawn, all participants will be offered breakfast/a snack in the PEAK Lab. Survivors will then complete survey questionnaires via REDCap first and physical assessments second, while caregivers will complete physical assessments first and questionnaires second.

6.8.3 Participants will be evaluated on skeletal muscle mass (bioelectrical impedance), heart rate variability, muscular strength (Handgrip Dynamometry, isokinetic knee flexion/ extension and shoulder diagonal), and aerobic capacity (6 minute walk test).

6.8.4 Following completion of all study procedures, dyads will be fully debriefed and given the opportunity to provide final feedback about the intervention in a meeting with the study chair. The two arms of the study will be explained and caregivers randomized to Arm 2 (survivor only EXCAP) will be provided an EXCAP exercise kit and a 45 minute instructional session in the use of the EXCAP exercises with an ACSM Certified Exercise Physiologist^{SM}.

6.8.5 Weekly phone calls or e-mails from a study team member, as detailed above, will desist when the participant's involvement in the study has ended, following the post-intervention assessment.

6.9 ***Costs/Payments*:** There will be no costs to survivors or caregivers for the physiological assessments (e.g. serum collection, bioelectrical impedance, and muscular strength), Resistance bands, Pedometers (or Fitness trackers), Actigraphs or Home-Based Walking and Progressive Resistance Exercise Prescription. All assessments, which are conducted and collected for research purposes only, will be paid for from funds controlled by Dr. Charles Kamen in the Cancer Control Unit within the James P. Wilmot Cancer Institute. Parking costs will also be covered.

Each participants will be paid up to $100 for taking part in this study ($200 total per dyad). Each survivor and caregiver will be paid $40 for coming to the baseline visit and $60 for coming to the

second visit. In addition, each participant will receive an exercise kit, including a pedometer and resistance bands, free of charge.

6.10 ***Return of Research Results*:** All data collected as part of this study will be for research purposes only. Should incidental findings arise during testing and that might have health consequences (e.g., involving heart rate or blood pressure findings), participants will be referred back to the physician who approved their entrance into the study.

At the end of the study, after all data have been collected, participants will be alerted of the study's overall findings.

7. SUBJECT CONSENT AND WITHDRAWAL

7.1 Current, state, federal, and institutional regulations concerning informed consent will be followed. Participation in this study is voluntary. Participants are free not to take part or to withdraw at any time, for whatever reason, without risking loss of present or future care they would otherwise expect to receive. In the event that a patient does withdraw from the study, the information they have already provided will be kept in a confidential manner. Participants may discontinue participation in the study at any time if they decide they do not wish to take part any longer. Participants may be withdrawn from the study by research personnel if it is deemed in their best interest to no longer participate.

8. REPORTABLE EVENTS

8.1 *Data and Safety Monitoring*

Clinical Trials Data Safety Monitoring Committee: The Director of the Cancer Center delegates responsibility for continued review and monitoring of all clinical trials conducted by the URCC to the Clinical Trials Data Safety Monitoring Committee. This committee provides oversight of study progress and safety by review of accrual and adverse events at annual meetings. Any adverse event requiring expedited review per protocol will be submitted to the Data Safety Monitoring Committee for determination as to whether further action is required.

The study PI and the study medical monitor determine if the adverse event requires expedited review. Interim meetings are scheduled, as needed, to address specific issues that require immediate attention to assure patient safety.

The Committee:

a) Reviews assigned clinical trials conducted at the URCC for progress and safety
b) Reviews all adverse events requiring expedited reporting as defined in the protocol
c) Reviews reports generated by the URCC data quality control review process
d) Submits recommendations for corrective actions to the Protocol Review Committee and the PI
e) In general, outcome data is not made available to individuals outside of the DSMC until accrual has been completed and all participants have completed the intervention. At this time, the DSMC may approve the release of outcome data on a confidential basis to the trial PI for planning the preparation of manuscripts and/or to a small number of other investigators for purposes of planning future trials. Any release of outcome data prior to the DSMC's recommendation for general dissemination of results must be reviewed and approved by the DSMC.

Safety Coordinator: The Medical Director of the Cancer Center Clinical Trials Office appoints the Safety Coordinator. The Safety Coordinator monitors adverse event rates utilizing the URCC Clinical Trials database. If any DSMC assigned study has had two or more of the same SAEs reported in a month or more than six of the same SAEs in six months, the DSMC will review the summary of SAEs, discuss events with the Study Chair, and conduct a more detailed review with the Study Chair. The Data Safety Monitoring Chair will determine if further action is required.

The Safety Coordinator:

a) Forwards all adverse events requiring expedited reporting to the Data Safety Monitoring Committee Chair who determines if immediate action is required
b) Maintains a database of all adverse events requiring expedited reporting
c) Insures all reports are available for all meetings of the Data Safety Monitoring Committee

d) Monitors adverse event rates utilizing the URCC Clinical Trials database.

8.2 ***Adverse Reporting Requirements:***

8.2.1 Adverse reactions to the EXCAP or EXCAP-PA Exercise Programs will be reported to the University of Rochester Medical Center IRB using the University reporting form and University of Rochester Medical Center adverse event reporting procedures.

8.2.2 Serious adverse events, while a participant is on study until 14 days after the date the participant goes off study, will be reported in writing to the IRB as per their requirements.

8.2.3 A serious adverse event is defined as any event that is fatal, life-threatening, disabling or incapacitating or results in hospitalization, prolongs a hospital stay or is associated with congenital abnormality, new cancer diagnosis or overdose.

8.2.4 This study will make use of the Common Terminology Criteria for Adverse Events (CTCAE), recommended by the National Cancer Institute. These criteria use five grades for adverse events. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

8.2.4.1 Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

8.2.4.2 Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

8.2.4.3 Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

8.2.4.4 Grade 4: Life-threatening consequences; urgent intervention indicated.

8.2.4.5 Grade 5: Death related to AE.

9. RISK/BENEFIT ASSESSMENT

9.1 ***Risks to participants:*** There are four potential risks associated with participation in the proposed study: 1) physical harm associated with assessment procedures, 2) physical harm associated with intervention procedures, 3) emotional distress and 4) loss of confidentiality.

9.1.1 In terms of physical harm associated with assessment procedures, risks associated with a 6-minute walk test are similar to participation in a moderate to vigorous walking exercise program and are minimal for individuals with no cardiopulmonary, orthopedic, or age identified risk factors as determined by a physician. Risks include muscle cramps, muscle strain and/or joint injury, delayed muscle soreness, lightheadedness, and fatigue. Handgrip Dynamometry and Biodex isokinetic tests for strength may cause minor stiffness and/or tenderness in muscles for a couple of days following testing. The nature of these assessments will require a level of exertion; this exertion may cause temporary changes such as an increase in heart rate and blood pressure, both of which are normal responses to vigorous exercise. There is a small risk of irritation to the skin from the electrodes used for the BIA analysis.

9.1.2 In terms of physical harm associated with intervention procedures, commencement of a moderate walking and progressive resistance exercise program is not associated with any severe side effects and risks are minimal for individuals with no cardiopulmonary, orthopedic, or age identified risk factors as determined by a physician. The absolute chance of a cardiac event among adults while engaging in vigorous exercise is one per year for every 15,000 to 18,000 people.[59] A transient increase in blood pressure may occur with all types of exercise. Although unlikely, a moderate walking and progressive resistance exercise program may also cause musculoskeletal effects, such as mild muscle soreness, a muscle strain, or other related accidental injuries such as tripping. Overall, the risk level for participation in the moderate intensity EXCAP Home-Based Walking and Progressive Resistance program is minimal.

9.1.3 In terms of emotional distress, the quantitative assessments explore issues associated with the relationship between survivors and caregivers, feelings about treatment, and mental health. The sensitive nature of these items may cause participants to become distressed as they think about their responses. Specific to research with dyads, during the intervention or possibly as a result of responding to questionnaire items, issues may arise that could lead to tension between survivor and caregiver and possible conflict and/or violence within the dyad.

9.1.4 In terms of loss of confidentiality, both quantitative data and biological samples from participants will need to be stored. Though rigorous and well-tested data safety and security guidelines will be observed, there is still a chance that confidentiality could be breached and sensitive medical information could become known to persons outside the research team.

9.2 ***Adequacy of protection against risk:*** Four potential risks have been associated with participation in this study: 1) physical harm associated with assessment procedures, 2) physical harm associated with

intervention procedures, 3) emotional distress and 4) loss of confidentiality.

9.2.1 Physical harm associated with assessment and intervention procedures: Every effort will be made to minimize the risks associated with study procedures for all participants. First, all participants (cancer survivors and caregivers) must have the approval of their physician to enter the study. All testing and exercise prescription discussions will be supervised by an American College of Sports Medicine (ACSM) Certified Exercise Physiologist[SM]. A physician (or physician's designee) will be present when necessary according to ACSM Guidelines; for example, in circumstances where the participants' physician has approved the participant to participate in the study, but review of a participant's medical history reveals cardiorespiratory, orthopedic, or central nervous system conditions that do not preclude participation in exercise but might increase the participant's risk of complications during fitness testing. This conservative policy is designed to ensure the safety and minimize the risk to cancer survivors. EXCAP uses standardized guidelines for exercise testing and prescription provided by the ACSM, which have been shown to be safe to use with medically ill populations.

Risks will also be minimized by following the documented and approved procedures for tests that are performed in the NIH-funded and approved University of Rochester General Clinical Research Center (GCRC); their trained staff will perform these tests. Specifically, to minimize the chance of bruising and the slight chance of infection associated with blood collection, the GCRC employs standardized hospital procedures for blood collection, and uses a trained phlebotomist and sterile materials.

Though the overall risks of participating in a low to moderate intensity home-based exercise program are minimal, participants will be instructed to stop performing the exercises if they experience cardiopulmonary symptoms that may be indicative of a more serious medical side-effect. An ACSM Certified Exercise Physiologist[SM] will be available by phone or e-mail to assist participants in problem solving and performing exercises in a safe fashion.

9.2.2 Emotional distress: Dr. Kamen has over ten years of experience conducting assessments with persons undergoing both acute and chronic stress, including individuals who report extensive trauma histories and are living with chronic illnesses, as well as combat veterans and their spouses. It is rare for a participant to find self-report questionnaires to be psychologically distressing, even when responding to items that have asked directly about trauma exposure and trauma symptoms. To prevent distress, participants will be informed that they are free to decline to answer any question for any reason; furthermore, these options will be explicitly stated in the consent forms. Research staff will be extensively trained to help minimize distress to participants. However, should participants become depressed, anxious, agitated, or otherwise distressed during the assessment, Dr. Kamen or another trained member of the research staff will be notified and the participant will be triaged and referred for care. Should the participant already be receiving care, they will be referred to follow up with their care provider and a check in call will be made following the assessment to establish participant safety and comfort. For concerns related to violence within the dyad detected during the course of the study, we will take the following precautions. As stated above, Dr. Kamen will be available at all times to provide

clinical crisis intervention. He has taken continuing education courses specifically focused on the assessment and treatment of domestic violence. In addition, a resource list will be available which will include emergency housing shelters, and programs, clinicians, and support groups specializing in relationship abuse and violence. For more minor relationship disruptions that may result from participation, we will have referral information available for therapists who treat dyads and families.

9.2.3 Confidentiality: This study involves collecting biological samples and obtaining access to medical records, and steps must be taken to protect both participant data and identity. The following confidentiality protection steps will be taken: 1) Research staff will participate in initial training, follow-up training, and ongoing monitoring and supervision to ensure understanding of the ethical issues involved in this research; 2) only the research staff will know the name, identification (ID) number, and contact information of participants. The list that links the participant's name with ID number will be kept on an encrypted drive accessible only by the research staff; 3) consent forms will be kept in locked filing cabinets in a locked office, again accessible only by research staff; and 4) any personal identifiers linked to data will be removed and replaced by non-identifying ID numbers in all records. The electronic files that contain quantitative data will be stored on a secure University of Rochester Medical Center file server. These files will be password protected and accessible only by the PI and the study coordinator.

Due to the dyadic nature of the proposed study, additional precautions are necessary to avoid inadvertent transfer of confidential information from one partner to another as a result of participation in assessments. Quantitative assessments are conducted separately with each partner so that it is not possible for research staff to reveal information to one partner about the other partner.

9.3 ***Benefits:*** There are no direct benefits of the study to the study participants. Potential secondary benefits of the study include that all participants will receive an exercise kit to keep at no charge. Caregivers in the individual intervention group will receive the kit and instructions after completing all of the study assessments. Participants may or may not receive any further benefit from participating in this study.

10. DATA COLLECTION AND MEASURES

10.1 *Psychosocial Questionnaire Measures*

10.1.1 Psychological distress will be evaluated using three measures. First, general mood (the **primary outcome**) will be assessed through the short form of the **Profile of Mood States (POMS)**. The POMS consists of 30 adjectives in 6 subscales (e.g., anxiety, depression), which participants rate on a five-point scale with "1" = "Not at all" and "5" = "Extremely" to describe their moods over the past week. The POMS has been used extensively in research with cancer patients and has demonstrated reliability and validity.[60,61]

10.1.2 Second, depression will be assessed with the **Patient Health Questionnaire (PHQ-9).** The PHQ-9[62] is a 9-item multipurpose depression scale developed and validated for use with a variety of populations. It incorporates diagnostic criteria for depression and is quick to administer. Its diagnostic validity and reliability have been tested in medical populations.[63] A total score of 10 or higher will be defined as a depressed case for analyses of possible subgroup changes in depression.[64] If there is concern about the degree of depression and/or possible risk of suicide based upon information from the PHQ-9, the participant will be referred to their physician and/or an appropriate source of psychological care.

10.1.3 Third, anxiety will be measured using the **Spielberger State/Trait Anxiety Inventory (STAI Form Y-1).** In order to reduce overall patient burden, we will use only the state portion of the questionnaire. This one-page, self-administered questionnaire consists of 20 short statements which people may use to describe their feelings. Participants are asked to fill in a numbered circle to indicate the degree to which they generally experience the particular feeling, ranging from 1 = "Not at all" to 4 = "Very much so" at that time. It is one of the most widely-used assessments of anxiety. Internal consistency coefficients > 0.90 have been shown, along with test/retest reliability coefficients > 0.70. Concurrent, construct, convergent and divergent validity have also been demonstrated.[65,66]

10.1.4 Quality of Life (QOL) will be assessed with the **Short Form Health Survey 12 (SF-12),** a 12-item, multi-purpose scale designed primarily to measure functional health and well-being in a parsimonious fashion.[67] For the current study, mental and physical health summary scores will be used to asses QOL. Responses are anchored using a Likert scale ranging from 1 to 5 (strongly agree, agree, neutral, disagree, and strongly disagree, respectively). Cronbach's Alpha coefficients indicate reliability of over .90.[68,69]

10.1.5 Support between the patient and caregiver will be assessed with three measures: the Dyadic Adjustment Scale-7; the Dyadic Support Questionnaire; and the Social Provisions Scale.

10.1.5.1 The **Dyadic Adjustment Scale-7 (DAS-7)** is a 7-item scale designed to measure how individuals feel about their relationship with their caregivers using a unidimensional

global approach. Responses are anchored on a Likert scale ranging from 1 to 5 (strongly agree, agree, neutral, disagree, and strongly disagree, respectively). Cronbach's Alpha coefficients indicate an internal consistency range from .76 to .87, and a test-retest reliability range from .63 to .85 among cancer patients.[70]

10.1.5.2 The **Dyadic Support Questionnaire (DSQ)** is an 18-item survey based on four functions of social support (emotional, appraisal, instrumental, and informational support). Nine items measure received social support, that is, support provided by the partner; nine additional items measure support provided to the partner. Items are anchored using a Likert scale ranging from 1 to 5 (from not at all to a great deal). Items are summed to create scales for received and provided support. Cronbach's alpha reliability coefficients range from .85 to .92, test-retest reliability coefficients range between .74 and .92 for this measure.[71]

10.1.5.3 The **Social Provisions Scale – Short Form (SPS)** is a 10-item survey designed to measure availability of emotional, tangible, and informational social support using a single general social support scale. Items are anchored on a four point Likert-type scale ranging from Strongly Disagree to Strongly Agree. Psychometric properties for the measure are excellent, with Cronbach's alpha reliability coefficients over .90.[72,73]

10.1.6 Additional patient-reported health outcomes will be measured with several short item banks from the **Patient-Reported Outcomes Measurement Information System (PROMIS)**. The PROMIS item banks were developed by a National Institutes of Health (NIH) cooperative group and tested extensively on multiple waves of participants. The item banks all display adequate reliability and excellent convergent validity with existing legacy measures (e.g., the FACIT-F). The current study will include items from the general health, anxiety, and fatigue banks.[74,75]

10.1.7 Sleep difficulties and fatigue will be assessed with two measures: the Insomnia Severity Index and the Multidimensional Fatigue Symptom Inventory.

10.1.7.1 Insomnia symptoms will be assessed using the **Insomnia Severity Index (ISI)**, a commonly used, 7-item psychometrically reliable and valid measure providing an insomnia total score and subscale scores in cancer survivors.[76,77]

10.1.7.2 Fatigue will be assessed using the **Multidimensional Fatigue Symptom Inventory (MFSI)**, a 30 item measure that assesses the impact of fatigue using five subscales: general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation.[78,79] Though developed to measure cancer-related fatigue, the scale has been used with non-cancer populations; items are generic and could apply to both patients and caregivers.[80-82] The MFSI is both valid and reliable, with Cronbach alphas for subscales ranging from .71-.86.[83]

10.1.8 LGBT-specific minority stress will be assessed with the **Heterosexism and Identity Questionnaire**, a 41 item measure with nine subscales assessing harassment, discrimination, acceptance, concealment, identity, and homonegativity. The principal investigator has used this

measure previously in studies of same-sex relationships, and it demonstrates acceptable reliability and validity.[42]

10.1.9 Finally, patient-physician interaction will be measured with a battery of short questionnaires: the **Perceived Efficacy in Patient-Physician Interactions** (PEPPI) scale, the **Stanford Self-Efficacy for Managing Chronic Disease Scale** (SSES) and **The Human Connection** (THC) scale. All three questionnaires are rated on a Likert-type scale, measure multiple aspects of patient empowerment and communication in the context of medical interaction, and have been used extensively in medical research.[84-86] Psychometric properties for these scales are excellent and participant burden is minimal.[85-87]

10.2 ***Physiological and Physical Activity Measurements***

10.2.1 Physical Activity will be assessed subjectively using the Physical Activity Readiness Questionnaire (PAR-Q+), the Aerobic Center Longitudinal Study Physical Activity Questionnaire and questions on the daily journal. In addition, objective assessments of physical activity will be obtained via actigraphy, from the pedometer, and through heart rate variability.

10.2.1.1 The **Physical Activity Readiness Questionnaire (PAR-Q+)** will be used following the consent process as an additional screen for medical contraindications to exercise. The PAR-Q+ asks about a variety of medical conditions and physical symptoms associated with contraindications to increased physical activity. Reliability (r=0.99) and sensitivity (0.90) are high when assessing hypertension and other risk factors for increased physical activity.[88] In addition to the PAR-Q+, all participants will receive medical clearance from their physician (or the study medical monitor, or designees) to participate in the exercise intervention.

10.2.1.2 The **Aerobic Center Longitudinal Study Physical Activity Questionnaire (ACLS)** is a measurement instrument that includes assessment of lifestyle physical activity.[89] The questionnaire requests that participants report their engagement in fourteen different physical activities (frequency, intensity and duration) over the last three months. Estimates of energy expenditure are calculated using the following equation: (sessions/week) * (min/session)* (hour/min) * MET [Note: MET = metabolic energy expenditure rate] for each activity and then summed to provide total MET hours of energy expenditure for a week. The index of walking, jogging, and running predicted treadmill performance time (beta = .31) and there is a moderate relationship between energy expenditure estimates and treadmill performance (r = .41).

10.2.1.2 The **Daily Diary (as referenced elsewhere in the protocol)** is designed to track daily physical activity. The participant will be asked to complete the journal each night immediately prior to sleeping and record steps walked, minutes of resistance training completed, and a Rating of Perceived Exertion. The daily diary will also include an item assessing average daily distress, rated on a 0-10 scale. All participants will complete this daily assessment of distress, but only those randomized to the exercise condition will complete the exercise-relevant measures.

10.2.1.3 **Actigraphy**, as an objective measure of physical activity, will involve the waist-worn actigraph. The actigraph provides calculated energy expenditure values for Active Energy Expenditure (AEE) in kilocalories and total energy expenditure in Metabolic Equivalents per Time (METs) in kilocalories/min/kg. The actigraph features a variable epoch length which can be set between 1 to 240 seconds and 16 MB non-volatile memory. "Non-volatile" means that even if the battery, which can log 4000 hours of runtime, becomes exhausted, the data remain intact. The actigraph AEE Algorithm is based on validation studies, copies of which are available upon request. Software supplied by the manufacturer will be used to determine bouts of moderate or higher activity during each assessment period (day -7 to day 0, day 35 to day 42).

10.2.1.4 The **Pedometer** (or fitness tracker) will be used to assess duration of physical activity via steps walked during the time out of bed. Both pedometers and fitness trackers provide visual feedback of number of steps walked, and so can be used in the same fashion. The PEAK Lab is in the process of transitioning from standard pedometers to wearable fitness trackers.

10.2.1.4 **Heart Rate Variability** (HRV) will be measured using the Firstbeat® Bodyguard 2 to assess the HRV at the beginning of the first and the sixth intervention session. To measure HRV, participants will sit quietly for five minutes in the PEAK Lab wearing the Bodyguard 2 leads attached to their side and upper chest. Five biomarker outcomes will be assessed. Two time domains will be assessed including **SDNN** (the standard deviation of all normal R-R intervals measured between consecutive sinus beats) and **RMSSD** (the root mean square of successive differences between adjacent normal R-R intervals). Three frequency domains will be assessed including **RSA** (Respiratory Sinus Arrhythmia), **LF** (natural log of low frequency, total spectrum power of all NN intervals between 0.04 to 0.15Hz), and **LF/HF ratio** (the ratio of Low Frequency Total Spectrum Power of all NN Intervals Between .04 to .15 Hertz to High Frequency Total Spectrum Power of all NN Intervals between .15 to .40 Hertz).

10.2.2 A **6 Minute Walk** test will be used to assess aerobic capacity. This is a modified but still maximal measurement using a 6 minute walk protocol, generating a valid assessment while ensuring participant comfort. Participants are given a short warm up and cool down walking protocol in the test walking area in the University of Rochester PEAK Laboratory. Participants walk for a total of 6 minutes and cover as much distance as they can during this time. Upon completion of the test, the total distance walked is used to calculate an estimate of aerobic capacity (VO_2max; Maximal Oxygen Consumption). A physician (or physician's designee) is available onsite in the hospital during testing of patients deemed high risk by the ACSM Certified Exercise Physiologist^{SM}, as outlined by the ACSM fitness testing guidelines.

10.2.3 Muscular fitness will be assessed using two measures: a handgrip dynamometer test and an isokinetic muscular strength test.

10.2.3.1 The **Handgrip Dynamometer Test** is a grip strength test used to assess the maximal voluntary contraction generated by the arm muscles. The test is administered with the

patient standing with the elbow joint angle held constant at 180 degrees and the medial distal humeral epicondyl held 2 inches from the torso. Trials will be performed in an alternating bilateral sequence, for a total of six attempts (three with each arm). The best score of the three trials will be used for right and left limbs to calculate static strength.

10.2.3.2 The standard **Isokinetic Muscular Strength Testing Protocol** will use the Biodex System 4 Pro, a multi-mode computerized isokinetic dynamometer. Muscular strength testing will involve isokinetic knee flexion/extension (lower body) and shoulder diagonal (upper body) movements. A certified ACSM Exercise Physiologist will provide a full orientation to the isokinetic machine including: aligning subject into position, setting range of motion, and conducting a warm up set. The Physiologist will be on hand throughout the test to ensure proper form and participant comfort. After the warm up set, participants will complete a single set of 10 repetitions of each movement (isokinetic knee flexion/extension and shoulder diagonal) per side. Participants will exert maximal force through their entire range of motion, moving at a set speed in degrees per second against the lever arm. Participants will also rest for approximately one minute between sets. This isokinetic protocol will allow us to measure peak torque, maximal work, total work, and average power for each movement. The Biodex System Pro 4 has been used successfully in over 1,000 research studies and is both safe and accurate in measuring muscular function.[90] Risks of using the Biodex System Pro 4 are comparable to using a fixed resistance machine and include potential muscle soreness and fatigue after the conclusion of the test (see section 9.1.1 and 9.2.1); this protocol uses a single set of repetitions per movement, however, to minimize the risk of fatigue.

For participants who are unable to complete the Isokinetic Muscular Strength Testing Protocol, a standard **7-10 Repetition Maximum Dynamic Strength Testing Protocol** will be used to estimate patients' 1-repetition maximums for the leg extension (quadriceps) and bench press (pectoralis and deltoid). The patients will receive a full orientation to the fixed resistance machines and proper lifting form by a certified (e.g., ACSM) certified professional. Participants will perform a light warm up consisting of 8 lift repetitions employing the lightest weight on the machine. After the warm up, patients will be given a 1 minute rest break. A weight will be selected by the exercise testing staff based on the ease or difficulty of completing the warm up for each patient and this weight will be lifted for 10 repetitions or until subjective fatigue. Alternating rest breaks (2-3 minutes) and lifting bouts will continue with the resistance weight being adjusted by the exercise testing staff until the patient reaches a level of resistance that results in subjective fatigue between 7-10 repetitions. Established algorithms employing the weight lifted and the number of repetitions completed will then be used to estimate the patients' 1-repetition maximum.[91]

10.2.4 Skeletal muscle mass will be assessed using bioelectrical impedance.

10.2.4.1 The **RJL Bioelectrical Impedance System** is a non-invasive, easy-to-administer and safe method of assessing lean body mass. BIA involves passing a small electrical current through the body and evaluating the reactance and resistance to flow, which are related to

fat-free mass (FFM) and total body water. Prediction of lean body mass from BIA is as reliable as skin-fold measurements and hydrostatic weighing. Participants lie supine on a flat surface for approximately 5 minutes prior to the test, to ensure a resting metabolic state. Electrodes are attached to the right hand (distal end of the 3rd and 4th metacarpal and distal end of the ulnar and radius), and the right foot (distal end of the 3rd and 4th metatarsal and distal end of the tibia and fibula). Skeletal muscle mass will then be calculated from the lean body mass.[92]

10.3 ***Serum Analysis***

10.3.1 All blood draws and serum analyses will be done on all study participants (cancer survivors and their caregivers). A total of approximately 34 ml of blood (around 2 tablespoons) will be drawn at each time point (baseline and post-intervention assessment). As stated above in sections 6.4.1 and 6.7.1, blood counts will be measured by standard CBC with differential procedures. These counts will be collected by the study team and kept in the participant's research file. The blood sample (approximately 4 ml) for blood counts will be drawn in 1 purple-top (EDTA heparin plasma) vacutainer by research personnel in the General Clinical Research Center.

10.3.1.1 Because this is a research and not a clinical care protocol, the CBC is collected only to inform assessment of biological endpoints. No clinical care recommendations will be offered to participants on the basis of their CBC. Should any question about the CBC arise, participants will be directed to speak with their medical provider.

10.3.2 Measurement of biological endpoints will be conducted in Dr. Janelsins' Cancer Control and Psychoneuroimmunology Laboratory in the Department of Surgery. Samples will be stored in freezers owned and maintained by Dr. Janelsins. Serum cortisol, serum amyloid A, and C-reactive protein will be measured by three separate ELISAs. Inflammatory biomarkers will be measured using multiplex assays.

10.3.2.1 As stated above in section 6.4.1, the blood draws for estimation of biological endpoint levels will use 2 red top tubes for serum (10 ml each, 20 ml total). These tubes will be inverted 3-4 times, allowed to clot for 30 minutes at room temperature, centrifuged for 10 min at 1500 x g and then frozen at -20c or -80c. The blood draw for estimation of biomarker genomics (i.e., mRNA concentrations related to production of cortisol, serum amyloid A, and CRP) will use 1 purple top EDTA-heparin tube (10ml total). This EDTA tube will be rocked 10 times, stored upright for minimum of 2 hours at room temperature and then frozen at -20c or -80c. All tubes will be drawn by research personnel in the General Clinical Research Center (GCRC), processed by a technician in the GCRC, collected by a study team member and then transferred to lab space maintained by Dr. Janelsins in the Department of Surgery for immediate storing of serum or plasma, respectively. Mr. Bryan Thompson is responsible for all storage and analysis of samples in this laboratory.

10.3.3 Blood samples collected after regular hours will be centrifuged by the GCRC technician, and samples will be stored temporarily (overnight) at an appropriate temperature in the secure laboratory until they are processed for long-term storage. For longer storage, the samples will be frozen at -20°C or below and kept in a secured -80c freezer.

10.3.4 All human biological materials will be disposed of in adherence with the University of Rochester Office of Environmental Safety Biosafety Level II requirements. All laboratories used in the current study have received appropriate biosafety certifications by the University of Rochester Institutional Biosafety Committee and undergo routine inspections. All patient samples will be de-identified before being stored.

11. CONFIDENTIALITY OF DATA AND DATA STORAGE

11.1 **Data Collection Table**

FORM	Baseline	Post Intervention
On Study Data (Demographic and clinical data)	X	
Clinical Record Information (Clinical data – ***survivor only***)	X	
Medication Form	X	
Physical Activity Readiness Questionnaire (PAR-Q+)	X	
Profile of Mood States (POMS)	X	X
Aerobic Center Longitudinal Study Physical Activity Questionnaire (ACLS; 15-item physical activity history measure)	X	X
Patient Health Questionnaire - 9 (PHQ-9)	X	X
Spielberger State/Trait Anxiety Inventory (STAI Form Y-1)	X	X
Short Form Health Survey 12 (SF-12)	X	X
Dyadic Adjustment Scale – 7 (DAS-7)	X	X
Dyadic Support Questionnaire (DSQ)	X	X
PROMIS Patient-Reported Item Batteries	X	X
Insomnia Severity Index (ISI)	X	X
Multidimensional Fatigue Symptom Inventory (MFSI)	X	X
Heterosexism and Identity Questionnaire	X	X
Physician Interaction (PEPPI, THC, and SSE**) Scales**	X	X
Physiological Fitness Test Evaluations (6 min walk test, handgrip dynamometry, isokinetic strength test, bioelectrical impedance)	X	X
Heart Rate Variability (Firstbeat Bodyguard 2)	X	X
Biological Endpoints (via blood draw)	X	X
Pedometer (or fitness tracker)	Continuous (for those exercising)	Continuous (for those exercising)
Actigraphy	7 days before	7 days before
Daily Diary	Continuous (for those exercising)	Continuous (for those exercising)

11.2 All hardcopy research records will be stored onsite in the University of Rochester Medical Center, in the Cancer Control Unit and the PEAK Lab of the James P. Wilmot Cancer Institute. The Cancer Control Unit is located in the Saunders Research Building, in an office suite secured by electronic key cards. The PEAK Lab is located in the medical center and is also secured by electronic key cards. Offices within the Unit and the Lab are again secured by key and data is kept in locked file cabinets. Electronic research records are stored on the University of Rochester Medical Center's password secured and

firewall protected networks. These are the same methods of security used for patient medical records. Human serum samples are stored in locked freezers, within locked and alarmed laboratories that are accessible by key codes and electronic card swipes. All study data will be kept for a period of at least 6 years after the study and all reports and publications are complete.

11.3 All data (information and human blood samples) collected for the current study will be used in post hoc analyses as appropriate. Blood samples will be banked and data will be used for future studies only with prior consent of participants (cancer survivors and caregivers). The consent form contains appropriate language related to biobanking and participants are given the option to have their samples banked or to have them destroyed following analysis of the study hypotheses. Participants' individual research records will not be shared with their treating physician, unless they provide consent or the patient's treating physician is a study physician, in which case they will have access to study data as a study co-investigator. Overall study results will be presented to participants, faculty and staff at the University of Rochester Medical Center after completion of the study. Study results will be presented at professional meetings and published.

11.4 The study team will assign a numerical Study ID to each participant once they have signed the consent form. Study forms and questionnaires will use this number and the participant's first and last initials as identifiers to ensure data integrity. Other identifying information will not exist on these forms. A complete list of study participants with study ID, name, and contact information will be maintained separately for the purpose of contacting participants for weekly phone call or e-mail reminders; this database will be maintained until the study is closed. This linkage information will only be accessible to the study chair, study investigators, and the individual responsible for maintaining the database.

12. RESEARCH INFORMATION IN MEDICAL RECORDS

12.1 Documentation of study participation will be included in the medical record by means of uploading a signed consent form to each cancer survivor's medical record, for those participants enrolled in the research study from Wilmot Cancer Institute/University of Rochester Medical Center. Participants' blood draw at the Clinical Research Center will also be noted in the medical record as an outpatient appointment. No further research-related information will be included in the medical record.

13. DATA ANALYSIS AND DATA MONITORING

13.1 Measures for the primary and secondary aims will be:

13.1.1 Cancer survivor's self-reported psychological distress (30 item POMS Total Score) at post-intervention (Primary Aim 1)
13.1.2 Cancer survivor's serum levels of stress-related biological endpoints (cortisol, serum amyloid A, C-reactive protein) at post-intervention (Secondary Aim 2)
13.1.3 Cancer survivor's received support from the caregiver (Dyadic Support Questionnaire) at post-intervention (Secondary Aim 3)
13.1.4 Cancer survivor's physical activity, as measured by actigraphy, at post-intervention (Secondary Aim 3)

13.2 Measures for the exploratory aim in caregivers will be:

13.2.1 Caregiver's self-reported psychological distress (30 item POMS Total Score) at post-intervention
13.2.2 Caregiver's serum levels of stress-related biological endpoints (cortisol, serum amyloid A, C-reactive protein) at post-intervention
13.2.3 Caregiver's received support from the cancer survivor (Dyadic Support Questionnaire) at post-intervention
13.2.4 Caregiver's physical activity, as measured by actigraphy, at post-intervention

13.3 **Data Analysis**

13.3.1 The primary outcome measure for this study is the cancer survivor's self-reported psychological distress, as assessed by the 30 item Profile of Mood States (POMS) Total score at the post-intervention time point (~6 weeks after baseline). The primary analyses will involve a comparison of EXCAP-PA relative to survivor-only EXCAP©® using analysis of covariance (ANCOVA). This procedure assesses the statistical significance of the difference in post-intervention mean between the two arms, controlling for baseline score and using intent to treat analyses with 30 evaluable survivors per arm. The comparison of EXCAP-PA to survivor-only EXCAP©® assumes a null hypothesis of no difference, using a two-sided alpha. We will use ordinary least-squares estimation and F-tests for testing the fixed effects. Primary aim analyses will treat the LGBT cancer survivor as the unit of analysis. The mean difference between groups with associated 95% confidence intervals will be estimated using the appropriate contrasts. This study will establish initial efficacy of the dyadic intervention and provide an initial effect size for the intervention that will inform the development of a larger Phase III trial.

13.3.2 Secondary analyses will use standardized procedures developed by Dr. Janelsins and the Rochester Human Immunology Core to measure serum levels of distress-related biological endpoints (serum amyloid A, CRP, cortisol) via ELISAs. The efficacy of EXCAP-PA relative to survivor-only EXCAP©® in improving markers of HPA axis functioning (cortisol) and early

inflammation (SAA, CRP) will be assessed using three separate ANCOVAs, each controlling for baseline biological marker values, and two ANCOVAs for dyadic support and intervention adherence. Since the secondary aims, relating to immune biomarkers of distress and provision of support within the dyad, are intended to gather preliminary efficacy data for the development of a larger grant submission, the secondary analyses will also examine mean change scores (i.e., baseline assessment subtracted from the post-intervention assessment), standard deviations, and correlations on these variables for the two study arms.

13.3.3 The current study is neither structured nor powered to permit true analysis of mediation. However, exploratory analyses will involve examining associations between outcomes of interest (distress and biological endpoints) and potential mechanistic factors (social support from a caregiver, adherence to the exercise intervention). Using the analysis techniques of Imai, I will evaluate whether change in social support and change in intervention adherence are associated with the effect of the intervention on psychological distress and biological endpoints linked with distress. This will involve generating a correlation matrix to test bivariate relationships. We will then conduct separate analyses for support and adherence with each outcome, using mixed effects ANCOVA models with arm, baseline distress or biomarker score, with/without support and adherence pre-post change scores as model predictor terms. We will also evaluate change in caregiver distress scores from baseline to post-intervention in the EXCAP-PA condition using paired sample t-tests, to examine whether caregivers benefit from supporting LGBT cancer survivors. We will also examine outcomes in L, G, B, and T subgroups and evaluate confounding and moderating factors. Because of the many exploratory analyses involved, any results will only be used for hypothesis generation.

13.3.3 Additional analyses will examine between group differences in the other outcome measures. These will include: physical activity (ACLS, Daily Diaries), aerobic capacity (6 minute walk test), muscular strength (handgrip dynamometry, isokinetic strength test), depression (CES-D), anxiety (STAI), minority stress (Heterosexism and Identity Scale), relationship satisfaction (DAS-7), and quality of life (SF-12).

13.4 **Missing Data**

13.4.1 We expect some attrition due to loss to follow up, declining follow up, or illness. We expect to retain 85% of the sample over the short 6 week period from pre- to post-intervention. This estimate is conservative, as a previous study of LGBT patients and partners retained 93% of a sample of 249 dyads after 15 months and Dr. Kamen retained 100% of participants in his feasibility trial. With 85% retention, recruitment of 70 LGBT survivors will mean that we will have a sample of 60 survivors (and 60 caregivers) at the post-intervention assessment.

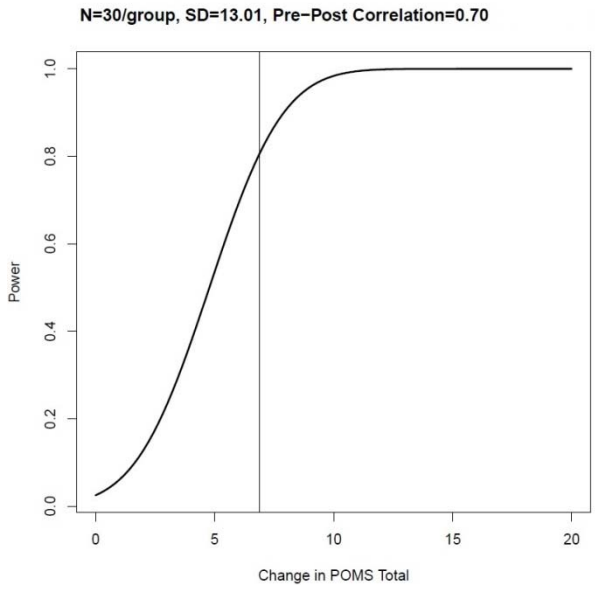
13.4.1 In the event that a participant willingly withdraws or is removed from the study by the investigator, any data already collected will be analyzed as deemed appropriate, unless the participant asks to have his or her data removed from the study. If a survivor or caregiver withdraws or is removed from the study following the baseline assessment, his/her partner may continue in the study.

13.4.2 Every effort will be made to encourage and facilitate provision of questionnaire and biological data. In the event of missing data, we will use intent-to-treat analyses and evaluate missing at random and missing not-at-random assumptions (MAR/MNAR) to determine the impact on results. We anticipate using multiple imputation if data are MAR and pattern-mixture models if data are MNAR.

13.5 **Sample Size**

13.5.1 The primary aim of this study is to evaluate influence of the partner vs. survivor-only exercise intervention on psychological distress in cancer survivors, as measured by the POMS total score at the post-treatment assessment. Based on previous research on EXCAP©® that we have conducted, and assuming a SD of 13.01 for the POMS total score and a correlation of 0.7 between baseline and post-treatment, we will have 80% power to detect difference of 6.90 (a moderate effect size of 0.58) between the two groups at the 0.05 level. The power curve in Figure 5 shows the statistical power we have to detect difference between the two treatment arms in changes from baseline to post treatment on the POMS total score should the proposed study yield smaller mean differences.

Figure 5: Model Power Curve



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APPENDICES

1. Letter from study team to cancer survivor's physician

2. Letter from study team to caregiver's physician

3. Intervention protocols

PEAK HUMAN PERFORMANCE CLINICAL RESEARCH LAB

Wilmot Cancer Institute
Department of Surgery
URCC NCORP Research Base
Cancer Control Research Program

MEDICINE of THE HIGHEST ORDER

CANCER SURVIVOR ELIGIBLE FOR STUDY

Your patient, _____, is eligible for the study: **Exercise Intervention for Cancer Survivors** (*PI: Dr. Charles Kamen*).

Your patient would like to participate in a study being conducted at the James P. Wilmot Cancer Institute of the University of Rochester. This study is being conducted by Dr. Charles Kamen, a clinical investigator in the Department of Surgery. This intervention is designed to see whether exercise can improve the health and well-being of cancer survivors and the health of their caregivers.

Please confirm that the patient has no physical limitations (e.g., cardiorespiratory, orthopedic, central nervous system) that contraindicate participation in maximal physiological fitness testing, and that you approve their participation in this fitness testing and a low to moderate intensity home-based walking and progressive resistance exercise program. Please also note there will only be an exercise physiologist present for this fitness testing, unless on review of the patient's medical history we feel that the presence of a physician (or their designee) is needed.

☐ **YES**, this patient is physically and medically able to participate in maximal physiological fitness testing and a low to moderate home-based walking and progressive resistance exercise program.

Physician (or physician's designee) Approval: _____

Date: _____

Thank you!

Charles Kamen, PhD, MPH
Assistant Professor
University of Rochester School of Medicine and Dentistry
James P. Wilmot Cancer Institute
Department of Surgery

Cancer Control Unit
601 Elmwood Avenue, Box 704
Rochester, New York 14642
(585) 275-5513 Fax: (585) 461-5601

PEAK HUMAN PERFORMANCE CLINICAL RESEARCH LAB

Wilmot Cancer Institute
Department of Surgery
URCC NCORP Research Base
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CAREGIVER ELIGIBLE FOR STUDY

Your patient, _____, is eligible for the study: **Exercise Intervention for Cancer Survivors** (*PI: Dr. Charles Kamen*).

Your patient would like to participate in a study being conducted at the James P. Wilmot Cancer Institute of the University of Rochester. This study is being conducted by Dr. Charles Kamen, a clinical investigator in the Department of Surgery. This intervention is designed to see whether exercise can improve the health and well-being of cancer survivors and the health of their caregivers. Your patient was a caregiver to an individual treated for cancer.

Please confirm that the patient has no physical limitations (e.g., cardiorespiratory, orthopedic, central nervous system) that contraindicate participation in maximal physiological fitness testing, and that you approve their participation in this fitness testing and a low to moderate intensity home-based walking and progressive resistance exercise program. Please also note there will only be an exercise physiologist present for this fitness testing, unless on review of the patient's medical history we feel that the presence of a physician (or their designee)is needed.

☐ **YES**, this patient is physically and medically able to participate in maximal physiological fitness testing and a low to moderate home-based walking and progressive resistance exercise program.

Physician (or physician's designee) Approval: _____

Date: _____

Thank you!

Charles Kamen, PhD, MPH
Assistant Professor
University of Rochester School of Medicine and Dentistry
James P. Wilmot Cancer Institute

Cancer Control Unit
601 Elmwood Avenue, Box 704
Rochester, New York 14642
(585) 275-5513 Fax: (585) 461-5601

Wilmot Cancer Institute
Department of Surgery
URCC NCORP Research Base
Cancer Control Research Program

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Department of Surgery

Cancer Control Unit
601 Elmwood Avenue, Box 704
Rochester, New York 14642
(585) 275-5513 Fax: (585) 461-5601

Intervention Protocols

Description of Standardized EXCAP©® Intervention Clinical Protocol Components

As noted above, each study participant randomized to either the EXCAP-PA or the EXCAP©® condition is provided with an EXCAP©® Exercise Kit, which includes a pedometer, resistance bands, two assist strap handles, a written manual, and a carrying bag.

The EXCAP©® program was designed by an Exercise Scientist certified by the American College of Sports Medicine (ACSM) and is in accordance with the guidelines for exercise testing and prescription as set forth by the ACSM. The prescription is also guided by the "ACSM Exercise Guidelines for Cancer Patients and Survivors."

The EXCAP©® Walking Prescription will be based on a patient's baseline pedometer assessment. Patients will be encouraged to increase their total steps walked each day by a minimum of 5% and a maximum of 20% each week, while maintaining a moderate intensity, during the 8-week intervention period. Patients will also be encouraged to continue increasing their steps and walking during the 3 months post-intervention. [Note: Walking intensity will be monitored via the Rating of Perceived Exertion (RPE) Scale, which is a visual analog scale ranging from 1 = no exertion to 10 = very strong exertion; this is part of the daily diary that participants will keep.]

The EXCAP©® Progressive Resistance Prescription will be based on a patient's optimal level of challenge. Patients will be instructed on the proper use of resistance bands. Patients will then be instructed to choose a resistance band with which they can perform 8-12 repetitions of 5 upper body resistance exercises and 5 lower body resistance exercises listed below. Patients will be instructed to begin with 1 set of 8-25 repetitions at a moderately challenging level (RPE 5-8) three days a week. Patients will be instructed to progressively increase to a minimum of 3 and a maximum of 4 sets for each exercise up to seven times per week. (Note. Patients will be instructed in the proper methods for performing each exercise).

The program consists of an initial 45-60 minute meeting with a certified exercise specialist. Participants will be shown the proper methods for performing the exercises and given a prescription for both walking and progressive resistance. A member of the study team will then follow up with weekly phone calls to the participants to check in on their progress, answer any questions, troubleshoot barriers and encourage patients to adhere to the exercise prescription. Our previous study provided the intervention over 4-6 weeks with excellent adherence and no adverse incidents.

Caregivers randomized to the survivor-only EXCAP©® condition will be instructed not to change their exercise behavior in any way.

A detailed list of the EXCAP©® exercises is provided below.

Aerobic (Progressive Walking)
Weekly increase in walking

Anaerobic (Progressive Resistance)

Squat
Side Bends
Leg Extension
Leg Curl
Toe Raises
Overhead Press
Biceps Curl
Triceps Extension
Chest Press
Rows
Core strength (crunches, planks)

Description of the EXCAP-PA Dyadic Framework Components

As noted above, survivors and caregivers randomized to the EXCAP-PA intervention arm will each receive EXCAP©® materials and be instructed in their use together.

The EXCAP-PA dyadic framework was developed by a clinical psychologist (Dr. Kamen) with a training background in dyadic behavioral interventions. This framework uses clinical skills from other dyadic interventions to train caregivers of LGBT cancer survivors in motivational strategies that can be used to help survivors adhere to the exercise program.

The program's three components are **discussion of LGBT specific stress**, **assessment of barriers**, and **elicitation of supportive behaviors**.

In **discussing LGBT specific stress**, the interventionist asks the LGBT cancer survivor open ended questions about experiences as a sexual minority individual seeking cancer care. The LGBT survivor will guide the discussion, but the interventionist may ask about how being a sexual minority affected relationships with care providers, unmet needs that arose during care, and how identity shapes experience of survivorship. The caregiver will then be asked to contribute any of their experiences in providing care for the LGBT survivor. Exercise is introduced in this context as a way the dyad can support one another, even in the stress of cancer or the stress of being a sexual minority seeking cancer care.

In **assessing barriers**, the interventionist asks both participants about the barriers that might interfere with their ability to exercise over the next week. Barriers could include daily obligations, physical concerns or symptoms, or emotional or motivational concerns. Both LGBT survivor and caregiver share their anticipated barriers with one another and with the interventionist.

In behavioral activation research, assessing barriers to accomplishing a behavioral goal is a well-validated method of ensuring goal completion.[93,94] The same technique is used in Motivational Interviewing, to elicit "change talk" and increase motivation to engage in the behavioral change.[95-97]

In **eliciting supportive behaviors**, the interventionist first turns the focus onto the LGBT cancer survivor, asking what behaviors by the caregiver would help to overcome the aforementioned barriers. Gentle Socratic questioning is used to refine the exact form of and rationale for these behaviors.

The interventionist then checks in with the caregiver, asking what behaviors the caregiver will try over this next week in supporting the LGBT survivor in overcoming barriers to exercise. Again, questioning is used to ensure that the caregiver knows exactly what behaviors would be most helpful. A final check with the LGBT survivor sets the collaborative goal and expectation for the week.

Supportive behavior exchange is a common technique in many dyadic interventions.[98-100] Typically behavior exchange techniques involve eliciting desired behaviors from each member

of the dyad on a weekly basis; however, in situations where one member of the dyad is a patient and the other a caregiver, supportive behaviors may be specifically directed at the patient from the caregiver.[101,102] This partner-assisted approach has been used previously in cancer control interventions, as well.[103-105103-105]

In weekly phone calls in the EXCAP-PA condition, the same intervention format is followed, with assessment of barriers followed by elicitation of supportive behaviors. These calls are always made with both the LGBT cancer survivor and the caregiver together to troubleshoot the past week's goal, establish a new goal for the week, and establish supportive behaviors that the caregiver will use.

In the survivor-only EXCAP©® condition, calls will be made to the LGBT cancer survivor alone and will involve troubleshooting and setting a goal for the next week, without the dyadic support component.