FORCE: Focus on Reducing Dose-Limiting Toxicities in Colon Cancer with Resistance Exercise

Study Protocol

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PROTOCOL SUMMARY

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PROTOCOL TITLE

1. Full Title: FORCE: Focus on Reducing Dose-Limiting Toxicities in Colon Cancer with Resistance Exercise

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PROTOCOL ABSTRACT

FORCE is a randomized home-based resistance training/strength training (RT) intervention study for Stage II and III colon cancer patients undergoing chemotherapy.

Participants will be 180 newly diagnosed Stage II and III colon cancer patients from Kaiser Permanente of Northern California (KPNC), the Penn State Cancer Institute (PSCI), and the Dana Farber Cancer Institute (DFCI). The intervention will begin by the third visit for adjuvant chemotherapy and continue exercise through the completion of post-operative chemotherapy. Specifically, we will examine between group differences for RT versus waitlist control for chemotherapy outcomes including dose delays, dose reductions, early stoppage and Grade 3 and 4 toxicities. We will also study changes in muscle mass (MM) and changes in specific inflammatory markers (e.g. CRP, IL-6 and TNF-RII) as potential markers of change in response to RT. To determine effects of change of MM on chemotherapy-specific drug clearance, we will examine the impact body composition changes on the pharmacokinetics (PK) of 5-FU and oxaliplatin, two of the most commonly used drugs for colon cancer.

OBJECTIVES

1. Primary Objective:
To examine differences in dose reductions, dose delays and early stoppage for chemotherapy and the total combined number of moderate and severe chemotherapy-associated toxicities between intervention group and waitlist controls.

2. Secondary Objectives:

a. To examine specific inflammatory markers (e.g. CRP, IL-6, TNF-α receptor II [TNF-RII]) in relation to baseline MM and fat mass (FM) and examine differences in changes in inflammatory markers between intervention group and waitlist controls. Inflammatory markers and body composition will be measured pre and post intervention.
b. To examine the impact of RT induced body composition changes on the pharmacokinetics (PK) of 5-FU and oxaliplatin between baseline and 4 months of RT.

3. d3 Creatine Objectives

a. To test whether resistance training during chemotherapy (v. control) increases d3 creatine muscle mass at 6 months.

b. To evaluate the association of d3 creatine muscle mass with changes in functional status and strength during chemotherapy.
c. To evaluate the association of d3 creatine muscle mass with chemotherapy toxicity and relative dose intensity.
d. To evaluate the association of d3 creatine muscle mass with cancer-related biomarkers, including inflammation, CEA levels and cardiometabolic risk factors.

BACKGROUND

1.1 Colon cancer epidemiology and prognosis by stage:

Colorectal cancer is the 4th most common in the United States, with an estimated 134,490 individuals being diagnosed in 2016, 71% located in the colon (versus rectum)[2]. Unfortunately, more than 49,190 individuals die from the disease annually, making colorectal cancer the second leading cause of cancer death in the United States. Surgery is the primary modality of management for colon cancer, and a 'curative intent' resection occurs in 80-85% of patients with non-metastatic disease (stages I-III). The benefit of adjuvant therapy has been consistently shown in multiple clinical trials, although the 5-year disease free survival for stage III disease is only 70%[3].

1.2 Adjuvant chemotherapy and dosing:

Beginning in 1990, an NCI expert panel recommended 5-fluorouracil (5-FU) and leucovorin (LV) as adjuvant therapy for patients with stage III colon cancer[5]. While initial studies tested a longer duration of treatment, the current standard is 6 months of therapy. An oral form of 5-FU, called capecitabine, has also demonstrated noninferiority as an alternative to IV 5-FU[6]. Select stage II patients, based on recurrence risk, are considered for adjuvant therapy as well. Further trials demonstrated a modest, but statistically significant, benefit to adding oxaliplatin to 5-FU/LV. The most common regimen is a 3 drug infusional combination called FOLFOX (5-FU/LV and oxaliplatin), now standard treatment for most stage III patients, considered in some stage II patients[4] as well as in stage IV/metastatic disease patients. Substitution of capecitabine for infusion 5-FU and leucovorin is another treatment regimen (CAPOX). Dosing of 5-FU/LV, capecitabine or FOLFOX is based on a standard formula that incorporates a patient's height and weight into a metric called, body surface area (BSA)[7]. Recommended milligrams per BSA were derived from trials testing for dose limiting toxicities (DLT), typically defined as severe (grade III or IV based on the NCI Common Toxicity Criteria [CTC] scale). While a standard starting dose is defined for each treatment option, many patients will still derive significant toxicities (Table 1). Issues with BSA dosing include the use of absolute weight without consideration of body composition or physiologic measures relevant for drug metabolism and disposition, such as renal and hepatic function. **Dosing based on BSA is limited in ability to reduce inter-patient variability in a drug's volume of distribution[8]**. Various drug elimination processes (e.g. metabolic breakdown or excretion) account for inter-patient variability in pharmacokinetics to a large degree[8]. Body composition (i.e. adipose tissue and muscle mass)[9] is another factor influencing pharmacokinetics and may predict toxic reactions to certain chemotherapy regimens[10;11].

Table 1. Select Toxicities associated with adjuvant therapy[4]

Toxicity	5-FU/LV		FOLFOX	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Neutropenia	40%	5%	79%	41%
Low platelets	19%	<1%	77%	2%
Nausea	61%	2%	74%	5%
Diarrhea	48%	7%	56%	11%
Neuropathy	16%	<1%	92%	12%

1.3 Toxicities of adjuvant therapy:

All 4 adjuvant therapy regimens have potential for multiple toxicities, including but not limited to gastrointestinal (e.g. nausea, emesis, diarrhea, abdominal cramping or discomfort), bone

marrow suppression (i.e. lowering white blood cells and thus immune system or platelets increasing bleeding risk), and fatigue and anorexia symptoms (Table 1). Oxaliplatin can lead to cold-induced and/or cumulative peripheral neuropathy, manifested as numbness, pins and needles, or pain in hands and feet, which can impact function.

1.4 Pharmacokinetics of 5-FU and oxaliplatin are altered by body composition:

Cytotoxic agents, such as fluoropyrimidine and oxaliplatin, are considered narrow therapeutic index drugs, where small changes in drug exposure can greatly impact clinical efficacy and toxicity. 5-FU is hydrophilic, but widely distributed through active transport[12]. It undergoes extensive metabolism, primarily through dihydropyrimidine dehydrogenase (DPYD), variants of which have been associated with increased risk of toxicity to 5-FU[13]. On the basis of these considerations, 5-FU clearance (CL) and volume of distribution (V) are likely related to body composition. Gusella *et al*. studied the PK of adjuvant 5-FU (425 mg/m^2 IV bolus) in 34 colorectal cancer patients[14] and determined that CL was significantly correlated with sex and fat free mass (FFM), while V was correlated with sex and Total Body Water (TBW). Overall, they concluded that CL of 5-FU was better predicted by FFM and TBW than by Body Surface Area (BSA)[14]. Thus, clearance of 5-FU is expected to increase (i.e. exposure decrease) in individuals with a higher FFM.

Body composition is also known to impact the PK of oxaliplatin. Oxaliplatin is eliminated renally, with clearance similar to glomerular filtration rate[15]. Quinney *et al*.[16] have previously reported that obesity is associated with an increased GFR as measured by clearance of iohexol. Thus, it is expected that oxaliplatin clearance may be increased in individuals with more adiposity and because it is also highly lipophilic, may lead to increased distribution in individuals with higher FM/MM ratios. In a population PK analysis of ultrafilterable oxaliplatin in 56 adults with metastatic disease, both CL and V were associated with bodyweight and individuals with higher body weights had larger exposure (AUC) to oxaliplatin[17]. To our knowledge, the effect of MM measured by DXA and change in body composition over time on PK of these drugs has not been examined.

1.5 Low muscle mass increases dose limiting toxicity:

The effect of low MM on chemotherapy treatment in several individual studies of different chemotherapy drugs and different cancer types have been explored. Cancer patients with identical BSA (i.e. 2.00 m^2) are highly variable in MM (range 30–70 kg)[18] and it has been hypothesized that low MM may result in a smaller tissue volume for distribution of cancer therapies, with potentially lower capacity for metabolism and clearance of drugs, leading to enhanced toxicity.

Figure 1 demonstrates among different cancer types, that patients with low MM behaved as if overdosed and had dose-limiting toxicity (i.e. of sufficient magnitude to require dose reductions, treatment delays or definitive termination of treatment). Relevant to this study, doses of 5-fluorouracil (5-FU) per kilogram of lean body mass (LBM) was associated with dose-limiting toxicity in stage II/III colon cancer patients and demonstrated that low LBM is a significant predictor of toxicity in patients administered 5-FU but only in females concluding that variation in toxicity between females and males may be partially explained by their differences in MM. Several other studies support LBM as an important determinant of chemotoxicity. In a study of French cancer survivors treated with FOLFOX regimens (Figure 2)[19], estimated mg oxaliplatin/kg lean body mass for this population cohort (*n*=58) varied from 2.5 to more than 6.0 mg/kg. A value of 3.09 mg/kg LBM was determined to be the cut point for dose-limiting toxicity (area under ROC curve=0.708). Toxicity rates were 0/17 (0.0%) and 18/41 (44.0%) using this cut point to separate the data into two groups (p=0.005; Fisher's Exact Test). In a retrospective analysis of 229 patients receiving FOLFOX4 for adjuvant chemotherapy following surgical resection of colon cancer, low psoas muscle cross-sectional area/height^2 (psoas index) was associated with an increased rate of grade 3-4 toxicity[20]. These combined results offer evidence that MM at initiation of chemotherapy may be an indicator of DLT and MM maybe be useful to individualize chemotherapy dosing.

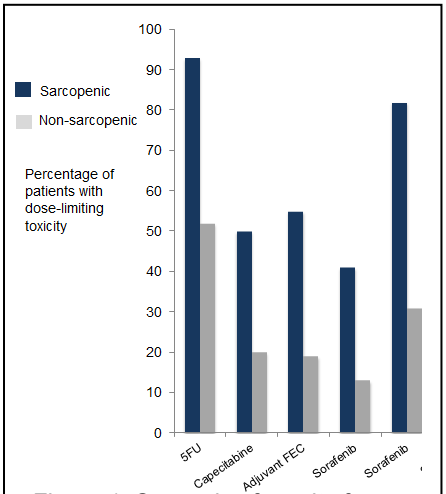


Figure 1: Synopsis of results from several studies relating treatment toxicity related to muscle mass during antineoplastic therapies[1]

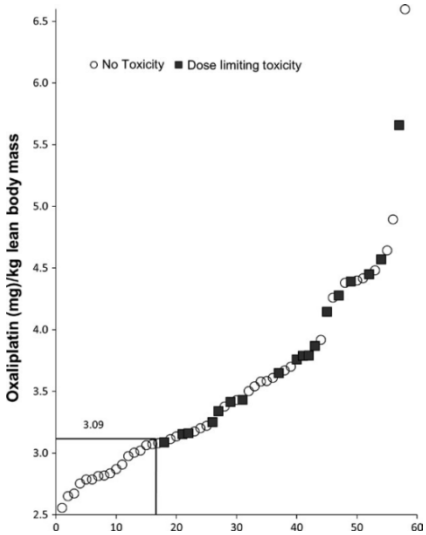


Figure 2: Distribution of the estimated oxaliplatin dose/kg lean body mass in French patients, from lowest to highest value.

Table 2. Rates and reasons for chemotherapy dose reduction in breast cancer patients

Characteristic	OnTrack (n=76)	Usual Care (n=77)
Patients requiring dose adjustments, No. (%)	9(12)	26(34)
Mean prescribed length of chemotherapy, days	119.2	116.7
Reasons for chemotherapy adjustment, No. (%)		
Neuropathy	3	6
Myelosuppression	2	3
Febrile neutropenia	0	6
Nausea and vomiting	2	3
Pain	1	3
Infection	0	3
Dyspnea	0	2
Obstipation/diarrhea	1	0
Average % dose reduction*	9.8	25.2

*Average dose reductions per group among participants needing a dose adjustment.

1.6 Dose limiting toxicities are associated with poorer prognosis:

Several studies across different cancers have demonstrated that either dose reductions or dose delays are associated with poorer overall survival (OS) or progression-free survival (PFS). Most relevant to this current study is a study that was designed to evaluate the impact of relative dose intensity (RDI), dose reduction, and schedule modification on outcomes in patients with

metastatic colorectal cancer (mCRC). Pooled datasets from two previous phase II trials of FOLFIRI (CCOG-0502; n=36) and mFOLFOX6 (CCOG-0704; n=30) in patients with mCRC were analyzed retrospectively. The median RDIs of irinotecan in FOLFIRI and oxaliplatin in mFOLFOX6 were 80 and 79%, respectively. Higher RDI of irinotecan in FOLFIRI was associated with significant improvements in PFS (9.9 vs. 5.6 months, P <0.01) and OS (26.7 vs. 12.9 months, *p*=0.01) and was the only independent factor associated with PFS (hazard ratio [HR] 8.48, *p*<0.01). Time delays of oxaliplatin was the only independent factor associated with PFS (HR 2.74, *p*=0.04)[21]. Numerous studies of women receiving chemotherapy treatment for ovarian cancer have also demonstrated that RDI, dose delays and dose reductions in chemotherapy regimens impact PFS and OS. In one of the largest multi-center retrospective studies of 325 women with FIGO stage III-IV epithelial ovarian cancer treated postoperatively with multi-agent intravenous chemotherapy between 1995 and 2009[22], delivered RDI <85% (hazard ratio [HR]=1.71; *p*=0.003) was associated with reduced OS.

1.7 Previous exercise interventions were successful in preventing dose reductions and improving chemotherapy completion rates:

To our knowledge, only a few previous studies have examined the effect of exercise on chemotherapy completion rates or in preventing dose reductions. In the most recent large study, a moderate to high-intensity, combined supervised resistance and aerobic exercise program (OnTrack) was compared to usual care (UC) in 230 breast cancer patients scheduled to undergo chemotherapy. Performance-based and self-reported outcomes were assessed before random assignment, at the end of chemotherapy, and at the 6-month follow-up. Those randomized to OnTrack required less chemotherapy dose adjustments (*p*=.002) had less nausea and vomiting (*p*=.031) compared with UC. Table 2 shows rates and reasons for chemotherapy dose reductions[23]. Similar non-significant results were observed in another small (n=33) study of CRC patients in Europe[24], however the sample size was too small for definitive results. In a second study of 242 breast cancer patients[25] those randomized to supervised resistance training during chemotherapy compared to usual care resulted in improved chemotherapy completion rate (*p*=.033). In a third trial of 30 women with recurrent ovarian cancer[26], a 12 week combined supervised and home-based exercise intervention during chemotherapy demonstrated that participants who completed the intervention had a higher relative dose intensity than non-completers (*p*=0.03)[25;26]. While three of the studies collectively demonstrate positive effects of exercise training during chemotherapy on completion rates and/or prevention of dose reductions in other cancers, only one small trial with inadequate power studied these effects in colon cancer patients, demonstrating a need to examine this in a group who experience significant DLT and a high prevalence of sarcopenia at diagnosis.

1.8 Inflammation, muscle mass and exercise:

Although the development of muscle wasting involves multiple contributors including neuropeptides, hormonal mediators, tumor- or pathogen-derived compounds, as well as various cytokines, the presence of inflammatory processes represents the primary requirement for the alterations in muscle protein synthesis and breakdown[27]. Recently, this observation was confirmed in a CRC cohort. Richard et al. reported an association between low skeletal MM index measured on CT scans and increased acute inflammatory response (i.e. high C-reactive protein and low albumin)[28]. In another study of 763 patients diagnosed with CRC undergoing elective surgical resection, multivariate logistic regression analysis showed that high neutrophil/lymphocyte ratio (NLR) (odds ratio [OR]=1.78 (95% confidence interval [CI]: 1.29-2.45), *p* <0.001) and low albumin (OR=1.80 [95% CI: 1.17-2.74], *p*=0.007) were independent predictors of reduced muscle mass[29]. A plethora of studies have investigated the role of the main inflammatory players in muscle wasting, such as tumor necrosis factor-a (TNF-a), interleukin-6 (IL-6), interleukin-1 (IL-1) and interferon-r (IFNr). These pro-inflammatory cytokines act directly or potentiate each other's actions at two key metabolic control points: the activation of ubiquitin-proteasome system[30] and inhibition of Akt/mTOR pathways[31], promoting protein

degradation as well as resistance to the anabolic actions, and ultimately leading to muscle loss. Several studies have now demonstrated that exercise reduces inflammation, through multiple mechanisms[32]. Specific to RT, an acute transient local *increase* in IL-6 is observed, which in turn results in a rise in anti-inflammatory markers locally to combat this rise, such as IL-10 and IL-1A, blunting the release of further inflammatory factors. This local effect then stimulates pro- and anti-inflammatory molecule secretion by other tissues, thus augmenting levels of systemic inflammation[33] . In cancer survivors the 12-week RT intervention in breast cancer survivors compared to relaxation control (n=103), blunted the marked rise in systemic levels of inflammation observed in the control group (IL-6, p=0.01 and IL6: IL-1ra ratio, p=0.02)[34].

1.9 Summary:

Since reductions in dose intensity of chemotherapy (both dose reductions and/or not completing planned number of treatments) are associated with lower survival in many cancers, identifying ways to maintain dose intensity are of tremendous clinical significance. Sarcopenia or low MM is a highly prevalent and an occult problem among newly diagnosed colon cancer patients and is associated with DLT. RT is known to increase MM, and increases in MM could reduce DLT with a potential impact on survival. This study may also provide evidence for consideration of dosing based on body composition. This study will fill many existing gaps in our understanding of body composition, RT and DLT.

2. OBJECTIVE

2.1 Primary Objective:

To examine differences in dose reductions, dose delays and early stoppage for chemotherapy and the total combined number of moderate and severe chemotherapy-associated toxicities between intervention group and waitlist controls.

2.2 Secondary Objectives:

2.2.1 Examine specific inflammatory markers (CRP, IL-6, TNF-α receptor II [TNF-RII]) in relation to baseline MM and FM and examine differences in changes in inflammatory markers between intervention group and waitlist controls.

2.2.2 Examine the impact of intervention versus control and RT-induced body composition changes on the pharmacokinetics [PK] of 5-FU and oxaliplatin between baseline and 4 months of RT.

2.3 d3 Creatine Objectives:

2.3.1 Test whether resistance training during chemotherapy (FORCE intervention group v. control) increases d3 creatine muscle mass at 6 months.

2.3.2 Evaluate the association of d3 creatine muscle mass with changes in functional status and strength during chemotherapy.

2.3.3 Evaluate the association of d3 creatine muscle mass with chemotherapy toxicity and relative dose intensity.

2.3.4 Evaluate the association of d3 creatine muscle mass with cancer-related biomarkers, including inflammation, CEA levels and cardiometabolic risk factors.

3. INTERVENTION

3.1 Rationale for home-based resistance training:

Resistance training increases muscle mass through hypertrophy of muscle cells[35]. A recent meta-analysis identified 11 resistance training intervention trials conducted within individuals with cancer[36]. In the six trials that evaluated intervention effects on MM, the weighted mean effect size was a statistically significant increase of 1.07 kg MM (p<0.0001). The interventions ranged from 12 to 52 weeks in length, 2 to 4 exercise sessions per week, with intensity described by percent of maximal (25-80% of 1 repetition maximum (RM)), or according to rate of increase (gradually, with the smallest available increment of resistance). The meta-analysis did not see further benefit of more than 2 sessions per week, and low to moderate intensity netted as much benefit as high intensity programs. Both women (n=818) and men (n=313) were represented in these trials and the beneficial effects were observed in both genders. Finally, more pertinent to the proposed work, a post-hoc analysis of data from a large resistance training trial in breast cancer survivors conducted by Co-PI Schmitz indicates that appendicular skeletal mass was better maintained in the intervention group who did twice weekly strength training when compared to usual care controls[37]. There have been fewer home-based resistance training studies than supervised or facility-based studies among cancer survivors. However, a systematic review on home based resistance training specifically for older adults demonstrated that home based resistance training programs can improve strength and functional ability[38]. Additionally, home based resistance exercise is generally well tolerated by cancer survivors and

has demonstrated benefits in physical function, strength and/or quality of life in patients with prostate cancer[39;40] and breast cancer[41-43].

3.2 Target population:

All newly diagnosed, Stage II and III, colon cancer patients within the first weeks of chemotherapy will be selected for participation in the study. Recruitment strategies will vary at each site (KPNC, PSCI, and DFCI).

3.3 Key inclusion criteria:

- Men and women ≥18 years
- Newly diagnosed with histologically confirmed stage II-III colon cancer
- Completed curative-intent surgical resection
- Currently prescribed one of the following adjuvant chemotherapy regimens: (IV 5-fluorouracil [5-FU] / leucovorin [LV], capecitabine, FOLFOX [5-FU, LV, oxaliplatin], CAPOX [capecitabine and oxaliplatin]
    - Patients must have started chemotherapy or plan to start, with planned receipt of the first exercise visit **by the third infusion visit**.
    - Patients receiving FOLFOX chemotherapy are eligible to enroll in the pharmacokinetics sub-study (see section 3.10).
- No planned major surgery anticipated in the intervention period
- Sufficient time to heal from any major surgery to start of intervention, including colostomy reversal (port-a-cath removal excluded)
- Creatinine value <2 mg/dL
- Approval by either oncologist or surgeon to participate in trial
- Readiness (as determined by the Physical Activity Readiness Questionnaire (PAR-Q) – see Appendix 13.2.2)
    - If there are any indications that home based exercise would be unsafe based on PAR-Q the patient will not be enrolled until confirmation from the patient's treating provider is received via email and/or phone that they are safe to exercise. Provider does not need to be contacted if patient answers 'yes' to 'Is your doctor currently prescribing any medication for your blood pressure or for a heart condition?'
- Ability to understand and the willingness to sign a written informed consent document in English
- Willingness to be randomized

3.4 Exclusion criteria:

- Concurrent actively treated other cancer (except non-melanoma skin cancer, in situ cervical cancer or localized prostate cancer treated with surveillance only)
- Patients with untreated hypertension (>180 mm Hg systolic or >100 mm Hg diastolic) appearing in the patient's medical record in the two weeks prior to screening will not be enrolled until confirmation from the patient's treating provider is received via email and/or phone that they are safe to exercise.
- Presence of metastatic disease
- Current strength training ≥2x week for the past 3 or more months
- Patients enrolled in other clinical trials of weight loss, physical activity or dietary interventions are ineligible.

3.5 Inclusion of women and minorities:

We seek to recruit 180 participants with a diagnosis of colon cancer. We will not exclude any participants due to their race and ethnicity. All races are accepted. The distribution of

participants by race and ethnicity is expected to mirror that of the institution's colon cancer patient population.

3.6 Patient recruitment, registration and randomization requirements:

Prior to initiating recruitment, each study site will obtain separate IRB approval from their respective institutions. Each collaborating site is under their own IRB's purview. Patient recruitment will be specific to each site. At all sites, participants must have the approval of a treating provider in order to participate in the study.

Kaiser Permanente Northern California recruitment:
At KPNC, potentially eligible study participants will be identified using the Electronic Medical Record (EMR) and a pathology database which is updated daily with newly diagnosed cancer cases. Additionally, oncology providers will be made aware of the study and will be asked for patient referrals at each Kaiser facility. Through the EMR, each stage II-Ill colon cancer patient will be identified close to the time of diagnosis and passively followed through surgery. After confirmation of chemotherapy prescription at the time of first oncology visit, the oncologist will be emailed through our secure internal email system to request approval for study participation for their patient and permission to contact the patient (see Appendix 13.1.1). Once permission is received from the oncologist, we will contact the patient through our secure internal email system and USPS mail, and then by phone to invite them to the study and to screen for eligibility using the above criteria. Contact information (i.e., email, address, phone number) will be identified using the EMR. The MD recruitment email, the participant recruitment email/letter and the recruitment phone script can be found in the Appendix 13.1.

Dana-Farber Cancer Institute recruitment:
Patients will be recruited from the patient populations of the Gastrointestinal Cancer Center clinics at Dana-Farber Cancer Institute. We will utilize multiple active recruitment techniques to maximize participation and generalizability. We will use the following strategies to identify potential participants

- Review of clinic schedules and patient lists for medical oncologists at Dana-Farber to identify patients with Stage II-III colon cancer. HIPAA waiver will be obtained to review these patient lists.
- Education of oncology providers of availability of protocol to encourage oncology providers to identify patients for study staff.
- Tumor registries at Dana-Farber
- Advertisements in patient areas

For potential participants identified through patient lists, we will contact provider and request permission to contact their patients. Providers will be asked to indicate any patients who should not be approached regarding participation in this study. Patients whose provider either provided permission to contact or who did not respond to email request will be assumed to be appropriate to approach. Once potential participants are identified, they will be contacted during next clinic visit or through mailing (see Appendix 13.1.2).

Interested subjects at Dana-Farber identified through these recruitment strategies will be screened by study staff either in person or by phone initially and if potentially eligible, he or she will schedule a visit with a member of the study staff to review the protocol and sign informed consent. All participants must have the approval of a treating provider in order to participate in the study.

Penn State Cancer Institute recruitment:
At PCSI, we will recruit by having a staff person review the EMR to identify potentially eligible patients. The study staff will approach the treating oncologist for permission to contact potentially eligible patients. Upon written (email) confirmation of permission to contact, the research coordinator will contact him/her by phone. During this phone call, the study will be briefly described, and study staff will ask if the patient would be willing to allow study staff to visit in person at the next clinic visit. Brief screening will also take place during this initial phone call (see Appendix 13.2). Patients found to be provisionally eligible based on this initial screening who are interested in hearing more will be visited in person by a study staff person to further discuss the trial and to proceed with the consent process if appropriate. Prior to starting recruitment, Co-PI Schmitz will visit the GI research conference and the GI tumor board meetings to describe the trial to the medical oncologists who treat colon cancer at PSCI and answer any questions they may have.

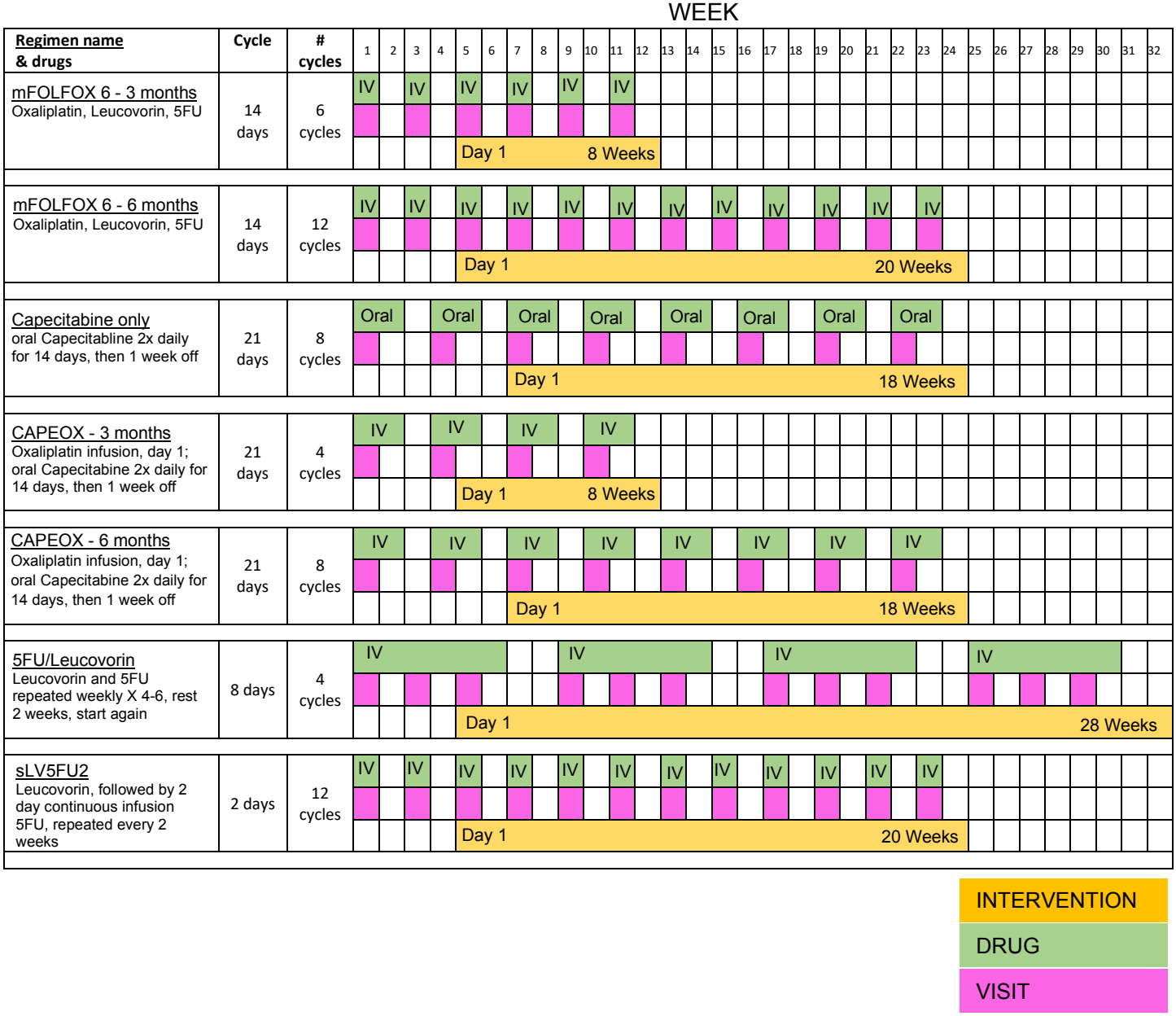
3.6.1 From Section D. Study overview of the original KPNC application approved 2017

3. How many participants will be enrolled in this study, or how many electronic records or medical records will be used? Provide your best estimate if you are not sure

Number of KPNC participants or records:	Approximately 115 participants to be enrolled
Records used:	Approximately 7500 KPNC records used
Number of non-KPNC participants or records:	Approximately 65 participants enrolled
Total number of participants or records:	Approximately 180* participants enrolled
	**Due to the impact of the COVID-19 pandemic on the study, we estimate that the total number of participants will be within the range of 10% above the original total of 180 participants.*

3.7 Enrollment and baseline testing:
Eligible participants who agree to participate will be scheduled for their first intervention visit at the earliest possible chemotherapy visit but by the third infusion visit. See Table 3 for details regarding the enrollment window based on the specific chemotherapy regimen

Table 3. Chemotherapy Regimens and Timeline



A research assistant will either conduct eConsent over the phone or by video conference or meet the participant in person to complete the consent forms. The baseline visit will most likely occur as an add-on to the first or second chemotherapy infusion session or another clinical appointment, so as to avoid the need for additional visits to the clinic or cancer center for the study. If scheduling of the baseline or follow-up visits at the clinic is not convenient for the participant, the research assistant will also be available to conduct these study visits at the participant's home.

After the participant consents to be in the study (see Appendix 13.3), we will complete questionnaires with the participant as part of the baseline visit (e.g. physical activity assessment and physical function testing, see Appendix 13.5, FFQ, see Appendix 13.6.1, SF-36, and demographics, see Appendix 13.4), as well as a patient-completed side effects questionnaire

(see Appendix 13.7.3). In addition, body composition will be assessed using anthropometrics collected at the baseline visit, a DXA (see Appendix 13.8) to be scheduled as soon as possible, prior to initial intervention, and creatine dilution (see Appendix 13.8.3). Also, at the baseline visit, we will arrange for research blood draw, when possible to be coordinated with clinical blood draw that the patient receives as part of clinical care (either that visit or next chemotherapy visit but prior to starting intervention).

3.8 Interventions for experimental group:

Table 4. Intervention Terminology

Chemotherapy Cycle	A cycle of chemotherapy from infusion visit to the next infusion visit, usually this will be 2-3 weeks
Chemotherapy Infusion Visit	Date on which the participant receives chemotherapy infusion at the cancer/medical center.
Exercise Session	A virtual meeting (except for one in person safety check) or in rare cases if patient does not have video access meeting in person between the exercise professional and the patient. In person will be scheduled on a day when participant has another clinical appointment. In rare instances, an appointment may need to be scheduled on a date and time other than an existing appointment.
Home Exercise Session	Exercise performed by the participant, at home with or without supervision by the cancer exercise professional

Exercise professionals are nationally certified, with expertise working with oncology patients.
Pre-In Person Training Visit Phone Call

1. The intervention begins with a telephone call between the trainer and the participant. The purpose of the call is to:
    a. Begin to build rapport with the participant
    b. Give them an overview of what to expect from the exercise training
    c. Begin behavioral counseling for motivating the participant to adhere to the training regimen
    d. Provide an opportunity for the trainer to ask about past experience with weight training, any injuries, surgeries or medical conditions that might impact the participant's ability to perform specific exercises.

At Exercise Session 1, the exercise professional will:

1. Teach the participant a warm-up and cool down routine.
    a. Teach the study specific exercises of the protocol (see Appendix 13.5.3). At the first exercise session, patients will be provided with the handouts for this session using the software SimpleSet Pro that will show pictures and explanations of the movements. Patients will also receive a simple exercise log and protein tracker for the duration of the study.
    b. A set of adjustable dumbbells and an aerobic step will be shipped to the participant's home. The FORCE Study will cover the cost of purchasing and shipping this equipment.
    c. Adapt the intensity of the exercises so that the load will fit with the individual physical ability of the patient and will follow the progression scheme in the table below.
    d. Patients will be instructed to consume one scoop of protein powder, with water, yogurt or milk or other foods about 30 minutes into their meal at 2 meals each day (see

Appendix 13.6.2). The FORCE Study will cover the cost of purchasing and shipping the protein powder.

e. Participants will receive a supply of the protein powder. The remainder will be shipped to their homes.
f. For exercise safety purposes, the first exercise session will happen in person, when possible. If not possible, the exercise professional may complete this session virtually by video conferencing. All study supplies (e.g., weights, handouts, exercise logs, protein logs, and protein powder) will be mailed to the participant's home.

2. The exercise and protein log will be used to track the adherence of the patient to the protocol. Patients will be taught to complete the exercise log on the days they perform the exercises at home, along with making any pertinent notes about the exercises and/or how they are feeling. Patients will be taught to complete the protein log daily.
3. Explain to patients that they should do in-home exercise sessions 2 times weekly until the next Exercise Session with the exercise professional. Patients will complete these exercises alone twice a week. After COVID-19, exercise professionals can offer to work-out virtually with participants once a week.

Table 5. Summary of exercise progression

	Exercise** Session 1	Exercise** Session 2	Exercise** Session 3	Exercise** Session 4	Exercise** Session 5	Exercise** Session 6
SETS	3	3	4	4	5	5
REPS	6	8	8	10	10	10
LOAD*	65%	65%	75%	75%	80%	80%- 85%
REST	30-60 secs	30-60 secs	30-60 secs	30-60 secs	30-60 secs	30-60 secs

*individualized to the patient's strength; **Prior to COVID-19, exercise sessions 1-6 are all in person. After COVID-19, exercise session 1 is in person and sessions 2-6 are virtual.

The exercise professional will meet with the patient for 4-6 Exercise Sessions that will coincide to the degree feasible with their regular infusion sessions. Prior to COVID-19, if scheduling of the Sessions at the clinic is not convenient for the participant, the exercise professional will also be available to conduct these visits at the participant's home. After COVID-19, only Exercise Session 1 is scheduled in person on a day when the participant a clinical appointment, and Sessions 2-6 are conducted virtually via video conferencing. If a participant is not capable of meeting virtually (e.g., lack of technology, internet access or tech skills), the exercise professional will meet the participant in person on the same day as a clinical appointment.

During each follow-up Exercise Session, the exercise professional will:

1. Collect and review the phone/visit log (these are the same questions asked during the weekly phone call) and exercise log to see what the participant did during the past weeks, discuss barriers, successes, and problem solve if needed. Participants can return logs either in person, over email or by text.
2. Collect and review the protein tracker to ensure that the participant is consuming adequate protein to build lean mass through resistance exercise. Participants can return logs either in person, over email or by text.
3. Visually evaluate the participant's ability to increase weight and adjust the amount of weight appropriately.

In between Exercise Sessions and after the initial 4-6 Sessions, the exercise professional will contact each participant 1 time per week either by phone or video and ask a series of questions

(see Appendix 13.5.5). These calls may be completed through the centralized calling center, by an exercise professional from one of the three study sites. Questions will assess adherence of the patient to the exercise regimen and the pattern of sessions with regard to time between sessions; protein supplement adherence; and any medical complications that prevented exercise sessions from occurring. A contact card will be mailed to participants when they are halfway through the intervention.

Table 6. Intervention Contacts

What	Number of times*	Aim	Time per session
Pre-In Person Training Visit Phone Call	1 time prior to 1st Exercise Session	Make introductions, orient participant to intervention, obtain health information on participant	20-30 min
Exercise Sessions	4-6 times, every 2-3 weeks during first 3 months of intervention	Learn and progress with exercise protocol	60 min
Home Exercise Sessions	2 times per week	Resistance exercise	45 min
Log Exercise	At-home exercise sessions	Log adherence	5 min
Log Protein Intake	Daily	Log adherence	5 min
Phone or Video Call	Weekly	Track adherence	5 min
Contact Card	1 time	Encourage participation, remind participants to return logs	n/a

*Each cycle is administered every 2-3 weeks

1. The exercise professional will speak with participants to review these exercise and protein logs each week, by phone or video conference, until the intervention is complete at approximately 6 months post initiation (corresponding to completion of adjuvant chemotherapy).

2. Study staff will then record the adherence of the patients to the exercise regimen and the pattern of sessions with regard to time between sessions, as well as any medical complications that prevent sessions from happening.

Intervention Goals:
Progressively higher weights for resistance training exercises conducted twice weekly throughout intervention) to achieve a 1-kg increase in lean body mass by the end of the intervention.

Intervention Standardization:
All exercise professionals will participate in a multi-day workshop. During this workshop, procedures of the intervention will be explained, and case studies will be presented and practiced. There will be monthly conference calls including all exercise professionals across sites, to monitor and discuss progress, problems and to monitor fidelity of the protocol. Telephone calls to intervention participants to encourage adherence will be scripted.

3.9 Enhanced safety procedures due to COVID-19:

As a result of COVID-19, exercise professionals will adhere to strict safety procedures when meeting with participants for the in person exercise sessions. Enhanced safety procedures include:

- phone screening before visits with COVID-19 script (Appendix 13.2.6),
- temperature checking when entering a clinical facility (KP only),
- both exercise professional and participant wearing face masks,
- frequent hand washing and hand sanitizing,
- maintaining a 6 ft distance when possible,
- frequently wiping down surfaces and equipment with disinfectant wipes, and
- any other appropriate precautions as required by local clinic and hospital procedures.

DFCI exercise professionals will be following DFCI COVID-19 policy for patients and staff while in the building.

3.10 Intervention for the waitlist controls:

Participants randomized to the usual care (U) group will be instructed to refer to their physician regarding what forms of exercise are safe for them, given their specific medical history. The U group will be told to continue whatever exercise program they have been undertaking up to enrolling in the study, but not to increase exercise or begin weight-lifting over the period of study participation (See Appendix 13.9). Participants will be sent a contact card halfway through the intervention reminding them of the follow-up visit. At the conclusion of participation, they will be offered: Emailed link to WebExercise routine; a set of resistance bands; a 30-minute interview with FORCE exercise professional; and a sample of protein powder.

3.11 Pharmacokinetics study:

Up to 30 individuals, who are scheduled to receive 6 months of 5-FU, leucovorin and oxaliplatin (FOLFOX), will be given the option to participate in pharmacokinetic (PK) testing (see Section 4.14), in addition to the randomized intervention.

3.12 Compensation:

All participants participating at Kaiser Permanente, Penn State and Dana-Farber who are not participating in the PK study will receive a gift card either in person or by USPS as a thank you for completing the baseline visit ($25) and the follow-up visit ($25). See Appendix 13.10 for example language to be included in thank card for those gift cards sent by mail. Patients participating in the PK study will receive a total of $225 in gift cards by study completion- $100 for each day that PKs are drawn and $25 for the follow-up visit (total 3 cards). In addition, parking will be validated on the 2 days that PKs are drawn.

3.13 Photographs of study subjects:

Participants will be asked if they would be willing to have their photograph taken. If they are interested, they will be asked to complete the Media Consent form. For those who consent, photographs of study participants will be taken during clinic visits (completing questionnaires, physical assessment testing, talking with study staff), to use in research presentations, for conferences and workshops, where the Investigator(s) present the study. Dana Farber Cancer Institute is excluded from this as they will not ask their participants if they are willing to be photographed.

3.14 Sharing of results with subjects:

All participants will be provided with whole body DXA results, both Baseline and Post-Intervention, after the conclusion of participation (See Appendix 13.8.5).

4. STUDY MEASUREMENTS

Initial screening will take place via telephone. At the in-person baseline visit, after the patient signs the consent form, s/he will undergo a series of baseline assessments, questionnaires and blood draws as described above. Many of the data collection instruments will be either data entered by a researcher or self-administered by participants into REDCap, which is a secure web application for managing online surveys and databases. The table below provides an overview of the measurements that participants will undergo over the course of the protocol and the timing of these measurements:

Table 7. Measurement Schedule

Measure	Screening	Baseline	Weekly	PK Cohort Only	Post-Intervention Visit[3]
Phone screening questions- PA screening and additional questions	X				
PAR-Q	X				
SF-36[4]		X			X
Demographics[4]		X			
Paffenbarger questionnaire		X			X
Physical function tests (balance, gait speed, sit and stand, grip strength)		X			X
Food frequency questionnaire[4]		X			X
Height, weight, waist and hip circumference		X			X
Whole body DXA		X		X[2]	X
Patient-completed side effects questionnaires[4]		X			X
D3- creatine dilution		X			X
NCI PRO CTCAE			X[1]		
Medical record review for chemotherapy dosing and toxicities			X		
Physical activity and nutrition logs			X		
Inflammatory markers		X			X
Pharmacokinetics (PK)				See section 4.14	
Injury history questionnaire[4]					X
Intervention follow-up survey					X

[1] At each scheduled intervention visit (for intervention arm) and thereafter by phone or secure web-link every time chemotherapy appointment is scheduled. For U group controls, an RA will administer by phone or secure web-link every time a chemotherapy appointment is scheduled.
[2] For PK cohort, a DXA scan will also occur at time of 2nd PK draw, at approximately 4 months after initiation of the intervention
[3] To be conducted within 2 weeks after last cycle of chemotherapy and end of intervention
[4] As a result of COVID-19, to reduce in person time participants will complete baseline and post-intervention questionnaires virtually. Study staff will email participants a secure web-link, send them home with paper copies to be mailed back within 3 days, or administer questionnaires over the phone.

4.1 Screening questionnaire:

Through a screening phone call, we will assess interest in and eligibility for the intervention. This will occur as soon as possible after the patient is scheduled for chemotherapy, ideally before initiation of chemotherapy. We will assess baseline physical activity eligibility by asking a series of physical activity screening questions (see Appendix 13.2.3) in order to ensure eligibility with regard to minutes of physical activity per week (eligibility= not engaging in current strength training ≥2x week for ≥3 months). Readiness will be determined using the Physical Activity Readiness Questionnaire (PAR-Q) (see Appendix 13.2.2). This latter survey was specifically designed to screen individuals for whom such unsupervised home-based exercise would be unsafe. These questions will be administered by a trained interviewer and those not meeting the eligibility qualifications (either already exercise too much or unsafe to exercise without supervision) will be reviewed by their treating oncologist and/or the study oncologist for advice on suitability of exercise intervention participation. We will also ask whether the individual has any planned major surgeries or is currently enrolled in other weight loss, physical activity or dietary studies (see Appendix 13.2.4). A researcher will record all screening question responses in an online REDCap form.

4.2 Demographic and health information:

Participants will be asked to complete a brief standardized survey regarding gender, marital status, household size, race and ethnicity, educational level, occupational status. In addition, cancer registry data and EMR will be reviewed for information on prognostic factors, including disease stage, nodal status, histologic grade, surgical procedures, and treatment medical history/comorbidities, cardiometabolic risk factors, including blood pressure. See Appendix 13.4.1. A researcher will record all relevant health information in an online REDCap form. Participants will complete an online REDCap survey about demographic information.

4.3 Medical outcomes study 36-Item, short form (SF-36):

A self-reported questionnaire consisting of 8 subscales that measure perceptions of general health, physical functioning, mobility limitations, pain, general mental health or emotional distress, and general social functionality. Response options allow participants to indicate the degree to which they feel healthy or impaired, with a score range of 0-100. Higher scores indicate a self-perception of better health than lower scores. See Appendix 13.4.2. Participants will complete the SF-36 in an online REDCap survey.

4.4 Physical activity and diet assessment:

We will use an abbreviated Paffenbarger Physical Activity (PA) Questionnaire to assess usual physical activity (See Appendix 13.5.1) and the 2014 Block food frequency questionnaire to assess usual diet (see Appendix 13.6.1). Participants will complete these questionnaires either on paper or via research assistant interview. Participants will fill out the PA assessment on paper, and then a researcher will enter their responses into an online REDCap form. Participants will complete the food frequency questionnaire on a paper scantron form.

Physical function tests include 4.5 to 4.8:

4.5 Balance test:

This test is conducted to measure participant's balance. Participants will be instructed to stand and maintain 3 different foot positions- side-by-side, semi-tandem and tandem- for 10 seconds each. (see Appendix 13.5.2). A researcher will use a stopwatch to keep time and record results from this physical function test in an online REDCap form.

4.6 Gait speed:
To measure locomotion, participants walk a short distance (4 meters) at their usual pace, completing one practice and two-timed trials. Scores are recorded as time in seconds required to walk 4 meters on each of two trials, with the better trial used for scoring. Tests will be administered by research staff trained in administering the test and in safety precautions. See Appendix 13.5.2. A researcher will record results from this physical function test in an online REDCap form.

4.7 Sit and stand:
To measure lower extremity muscular strength and endurance, the time required to complete 5 full stands from a seated position will be recorded using a stopwatch. One practice stand will be performed for positioning and learning of the task[49]. Tests will be administered by research staff trained in administering the test and in safety precautions. See Appendix 13.5.2. A researcher will record results from this physical function test in an online REDCap form.

4.8 Grip strength:
Grip strength is measured in both hands using a hydraulic grip strength dynamometer at baseline and at the post-intervention visit. If the participant reports current flare-up of pain in one wrist or hand, or has undergone fusion, arthroplasty, tendon repair, synovectomy, or other related surgery in the past 3 months, only the other hand should be tested. Other possible temporary discomfort during the test itself, there are no known risks for the participant. To measure upper extremity muscular strength, a Jamar hand grip will be held at the side of the body in a handing position with the elbows slightly bent. The dynamometer will be squeezed with as much force as possible over three trials with 20 seconds rest in between trials. Tests will be administered by research staff trained in administering the test and in safety precautions. Patients will complete the test 3 times with each hand, and the research staff will record the test results and note the patient's dominant hand. See Appendix 13.5.2. A researcher will record results from this physical function test in an online REDCap form.

4.9 Medical record review:
Details of each patient's health history, including medical imaging, comorbidities and colon cancer diagnosis and treatment details will be extracted from the EMR. In addition, laboratory and clinical data about the colon cancer tumor marker Carcinoembryonic Antigen (CEA) and cardiometabolic risk factors blood glucose, lipids, blood pressure and medication usage conditions will be extracted from the EMR. See Appendix 13.2.1. A researcher will record all relevant medical variables in an online REDCap form. In addition, CT scans will be obtained from the participant's medical record. KP scans will be stripped of PHI and analyzed at DOR. Penn State and DFCI scans will be stripped of PHI and transmitted directly to DOR via SFT. CT scan closest to the date of diagnosis but before chemotherapy will be colored using TomoVision sliceOmatic software to determine body composition, including muscle attenuation.

4.10 Body composition and body size:
At the baseline visit and at the follow-up visit, a DXA scan to assess body composition will be performed (see Appendix 13.8.2). All DXA scans will be performed in the total body scanning mode. A third scan will take place after 4 months for the subset of people participating in the PK study to correspond to timing of the 2nd PK blood draws.

At the baseline visit and at the follow-up visit, d3-creatine dilution will be used to accurately assess total body skeletal muscle mass (see Appendix 13.8.3).

Height and weight will be assessed using a scale mounted stadiometer and digital scale (or per institutional clinic standards) to the nearest 0.1 cm and 0.1 kg. Waist circumference and hip

circumferences will be measured at standardized landmark with participants dressed in light indoor clothing without shoes. Height will be assessed at baseline only. A researcher will record anthropometric measurements in an online REDCap form. See Appendix 13.8.1.

Because of COVID-19, if a participant doesn't feel comfortable with study staff touching him/her for waist or hip circumference measures, the study staff can teach the participant how to self-measure while observing and recording results in REDCap.

4.11 Dose reductions/delays and early discontinuation of treatment:
At the initiation of adjuvant chemotherapy, we will ascertain planned treatment course for participants, including planned cumulative dose and planned treatment duration. We will then examine the EMR for changes in chemotherapy dose and timing. The following variables will be defined for each drug administered:

- Planned dose intensity (mg/week) = planned total dose / planned duration of therapy (weeks)
- Actual dose intensity (mg/week) = actual total dose (mg) / actual duration of therapy (weeks)
- Relative dose intensity (RDI) (%) = actual total dose intensity / planned total dose intensity
- Average relative dose intensity (ARDI) (%) = the average across all regimens of the relative dose intensity
- Number of cycles of chemotherapy and date of initiation of each cycle

In addition, we will report on early stoppage by calculating actual number of cycles / planned number of cycles of adjuvant therapy. We will only consider dose reductions that occur after start of intervention. Chemotherapy treatment forms will be used to capture data from the EMR on chemotherapy administration (see Appendix 13.7.4). A researcher will record all relevant chemotherapy treatment variables in an online REDCap form.

4.12 Chemotoxicity:
Total combined number of moderate and severe chemotherapy-associated toxicities, assessed via medical record review, patient-completed NCI PRO-CTCAE and patient-completed side effects questionnaires. As shown in the Appendix, we will use a series of validated questionnaires for chemotherapy-associated side effects including NCI PRO-CTCAE and a questionnaire on neurotoxicity utilized in a recent phase III trial with oxalipatin[48]. See Appendix 13.7. Throughout the intervention, the research manager or assistant will email a secure web-link to the patient requesting completion of the NCI PRO-CTCAE questionnaire in advance of his/her next chemotherapy infusion visit. A researcher will record all relevant chemotoxicity variables in an online REDCap form. Participants will complete the patient-completed side effects questionnaire and NCI PRO-CTCAE questionnaire in online REDCap surveys.

4.13 Inflammatory blood measures:
All participants will undergo measurements of inflammatory markers around the time of the baseline clinic visit and the follow-up clinic visit. Blood will be drawn at each time point in a standardized fashion. A total of three tubes of blood (one 8.5 ml SST red-top tube for serum and two 6 ml EDTA purple-top tubes for whole blood and plasma) will be collected from all participating patients.

Tubes will be prepared and stored at local sites until completion of study. Each site will maintain a log of all collected specimens. At the completion of the study, the participating institutions will submit that log to the coordinating center for verification that each participant had required samples. Upon completion of the study, samples will be shipped to the laboratory of Dr. Jeffrey Meyerhardt, a FORCE PI at Dana Farber Cancer Institute, where his staff will inventory,

aggregate, and freeze samples until samples required for assays are shipped to Dr. Nader Rifai's laboratory at Boston Children's Hospital. The combined log (with deidentified study ID and sample numbers only) will be submitted to respective testing labs to ensure all samples are received. Any additional or unused samples will be returned to and collectively stored at Dana Farber Cancer Institute until needed for future studies.

Collection and Processing

1 x 8.5 ml SST red-top tube will be collected at baseline and follow-up visit.

- Invert tubes 5 times to initiate clotting
- Allow blood to clot for a minimum of 30 minutes, but no longer than 2 hours.
- Centrifuge 15-20 min at 3000 RPM (1100-2000 x g) at room temperature or 4°C.
- Aliquot the serum (top layer) into 4 cryovials (800 ul aliquots) per tube of blood. Label as serum.
- Freeze samples at -70°C
- Batch ship on dry ice.

2 x 6 ml EDTA purple-top tubes will be collected at baseline and follow-up visit.

- Gently invert the tube 8-10 times to mix the EDTA.
- Centrifuge 1100-1300g for 10 min (swing-bucket) or 15 min (fixed-angle) at room temperature or 4°C.
- Aliquot the top layer (plasma) into 4 cryovials (800 ul aliquots). Label as plasma.
- Aliquot the bottom layer into 2 cryovials (800 ul aliquots). Label as buffy coat.
- Freeze samples at -80°C.
- Batch ship on dry ice.

Assays for inflammation markers will be conducted in the laboratory of Dr. Nader Rifai at Boston Children's Hospital. High Sensitivity C-Reactive Protein (hsCRP): The concentration of CRP will be determined using an immunoturbidimetric assay on the Roche P Modular system (Roche Diagnostics - Indianapolis, IN), using reagents and calibrators from Roche. Interleukin-6 (IL-6): IL-6 is measured by an ultra-sensitive ELISA assay from R & D Systems, Minneapolis, MN. The assay employs the quantitative sandwich enzyme immunoassay technique. TNFα-receptor II: TNF-RII is measured by an ELISA assay from R & D Systems. The assay employs the quantitative sandwich enzyme immunoassay technique.

4.14 Pharmacokinetic (PK) measurements:

5-FU and oxaliplatin plasma PK will be determined during the first cycle of FOLFOX following study enrollment and during the FOLFOX cycle at approximately 4 months post enrollment Blood samples (5 mL, EDTA treated tubes) will be obtained from each patient at the following seven time points on each study day: prior to OX infusion; at the end of OX infusion (before 5-FU); after 5-FU loading dose (but before 5-FU infusion); approximately 0.5, 1, 2 hours after the start of the 5-FU infusion; and at the end of the 5-FU infusion (approximately 46 hours). For samples obtained up to 4 hours after the start of 5-FU infusion, an intravenous saline lock catheter will be placed in the participant's forearm. A minimal waste sample (<2 mL) will be obtained prior to each study sample. Less than 60 mL (about ¼ cup) total of blood will be withdrawn during each of the two phases.

Samples will be immediately processed to plasma, labeled with the study ID and sample ID (i.e., PK1 and collection time) and stored at -80°C until analysis. Samples will be shipped on dry ice

to the Clinical Pharmacology Analytical Core (CPAC) at the Indiana University Melvin and Bren Simon Cancer Center (IUSCC). Each site will maintain a log of all collected specimens. When the site is ready to ship samples, they will submit that log (with anonymized study ID numbers and time point only) to the CPAC for verification that each participant had the required samples. See Appendix 13.8.6 for a summary of the KP PK blood draw protocol.

Samples will be analyzed for oxaliplatin and 5-FU (and metabolite) concentrations in plasma using validated LC/MS/MS assays. A qualified analytical method will be developed by CPAC using internal standardization, liquid-liquid extraction, and UPLC-MS/MS (e.g. API 5500 QTrap, Applied Biosystems). The method development includes the infusion of the compound of interest (COI, i.e. OX, 5-FU and metabolites) with multiple mobile phases to identify a Q1 and Q3 that will maximize detection, chromatography in the selected mobile phases to maximize separation, selection of an appropriate internal standard, stability testing, the extraction of the COI from plasma by testing multiple acids/base and solvents, and linearity of an extracted standard curve and quality controls of the COI prepared in human plasma. The targeted lower limit of quantification is 1ng/ml using 20 µl of sample. CPAC has successfully used this sequence of studies to develop methods to quantify 57 new chemical entities and 75 clinically approved drugs.

A researcher will record all relevant PK variables in an online REDCap form.

4.15 Injury history questionnaire:

During the post-intervention visit, participants will be asked to complete a one-time questionnaire in REDCap detailing any recent emergency room visits or injuries since the start of the FORCE study. Injuries specifically focus on those that might be related to physical activity such as joint pain, soft tissue pain, chest pain, headaches, dizziness, nausea and abdominal pain (see Appendix 13.7.6).

4.16 Intervention follow-up survey:

During the post-intervention visit, intervention participants *only* will be asked to complete a one-time questionnaire in REDCap detailing their experience engaging with the exercise professional virtually (Appendix 13.4.3). This survey will only be collected with participants who enrolled in the study after the start of the COVID-19 pandemic.

4.17 Enhanced safety procedures due to COVID-19:

As a result of COVID-19, study staff will adhere to strict safety procedures when meeting with participants in person for the baseline and follow-up clinic visits. Enhanced safety procedures include:

- phone screening before visit with COVID-19 script (Appendix 13.2.6),
- temperature checking when entering a clinical facility (KP only),
- both study staff and participants wearing face masks,
- frequent hand washing and hand sanitizing,
- maintaining a 6 ft distance when possible,
- frequently wiping down surfaces and equipment with disinfectant wipes,
- allowing the option for participants to self-administer measurements that require touching with staff observing and recording results, and
- any other appropriate precautions as required by local clinic and hospital procedures.

DFCI study staff will be following DFCI COVID-19 policy for patient and staff while in the building.

5. POTENTIAL RISKS AND CHARACTERISTICS

5.1 Exercise:

There is the possibility of muscle soreness and injury from the exercise training program. The muscle soreness may last several days after the testing and after each exercise training session, but it is not likely to be severe enough to limit any usual daily activities. There is also a risk of muscle injury from the exercise training program. Muscle injuries may require medical attention, may take several months to heal, and may limit usual daily activities for a period of days, weeks, or months. It is expected that all study participants will incur at least minor muscle soreness over the course of the entire intervention.

5.2 DXA scan:

The cumulative radiation exposure from this test is considered small and is not likely to adversely affect disease status.

5.3 D3-creatine dilution test:

There are no known risks.

5.4 Blood draw:

Local pain, bruising, and, in rare instances, an infection might occur at the site where blood is drawn. There is also the possibility of dizziness or fainting while blood is being drawn.

6. ADVERSE EVENTS

6.1 Chemotherapy toxicity

As differences in chemotherapy-associated toxicities are part of objectives of the study, chemotherapy-associated toxicities will be monitored and recorded throughout chemotherapy period. However, severity and grading will not require reporting to IRB as those would be expected with standard of care treatment.

6.2 Adverse events and serious adverse events

Any unfavorable or unintended medical or psychological event experienced by a study participant during clinical research, sometimes referred to as an adverse experience or adverse effect. An AE can represent a new symptom or an exacerbation or worsening of an existing condition. It is not necessarily causally related to or associated with the investigational agent or protocol.

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures;
- Elective or pre-planned treatment for a pre-existing condition that did not worsen;
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission; and
- Respite care.

6.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

6.3.1 Expected adverse event:

Expected adverse events are those that have been previously identified as resulting from the intervention. For the purposes of this study, an adverse event is considered expected when it appears in the informed consent document as a potential risk.

6.3.2 Unanticipated problem (UP):

Any incident, experience, or outcome that meets **all** of the following reporting criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research where *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures or interventions involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

PIs must report UPs involving risk to subjects or others to the IRB.

6.3.3 Attribution:

Attribution is the relationship between an adverse event or serious adverse event and the study intervention. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study intervention.
- Probable – The AE is likely related to the study intervention.
- Possible – The AE may be related to the study intervention.
- Unlikely - The AE is doubtfully related to the study intervention.
- Unrelated - The AE is clearly NOT related to the study intervention.

6.3.4 Procedures for AE and SAE recording and reporting:

6.3.4.1 The PI or designee will investigate and analyze any event or incident to determine whether it is reportable to the IRB.

To determine whether an event or incident is a reportable UP, the PI or designee must answer and comment on the following **three** questions:

1. Is the event or incident unexpected in nature, severity, or frequency?
Evaluate whether the event or incident is described as a risk in the research application, investigators' brochure, or informed consent document and outside the expected severity or frequency.

2. Is the event or incident related or possibly related to participation in the research?

Evaluate whether the event or incident could reasonably have been caused by participation in the research.

3. Does the unanticipated incident, experience, event, and/or outcome suggest, in the PI's opinion, that either:
   a. The research places subjects or others at a greater risk (including physical, psychological, economic, or social harm) than was previously known or recognized; **or**
   b. This incident has more than a minimal effect on the integrity of the study or research results?

Determination 1: If the answer to **all three questions** above is "Yes," the event or incident is a UP and must be reported to the IRB. See PI Reportable Event and Incident Requirements SOP KPNC-502 for timeframe to report upon discovery.

Determination 2: If any answer is "No," the event or incident is **not** a UP and does not have to be reported as a UP; **however**, analysis is required to determine if reporting should be made as a different type of reportable event or incident (e.g., noncompliance).

6.3.4.2 All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the appropriate study-specific case report forms.

6.3.4.3 The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

6.4 Reporting requirements:

6.4.1 Each participating investigator is required to abide by the reporting requirements set at their individual sites.

6.4.2 Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the Kaiser overall principal investigator.

6.4.3 Serious adverse event reporting:

All serious adverse events that occur after the initiation of study intervention, during intervention or within 30 days after completion of intervention must be reported to the Kaiser Permanente overall principal investigator using the individual site's SAE form. This includes events meeting the criteria outlined in Section 6.2, as well as the following:

- Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) events – Unless expected AND specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Participating investigators must report each serious adverse event to the Kaiser Permanente Overall Principal Investigator within 24 business hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 business hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Bette Caan, DrPH
Division of Research
Kaiser Permanente
2000 Broadway
Oakland, CA 94612
510-891-3719
Bette.caan@kp.org

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

6.4.4 Reporting to the Institutional Review Board (IRB):

All unanticipated serious adverse events should be reported to the Kaiser Permanente IRB as defined by the PI Reportable Event and Incident Requirements SOP KPNC-502. Other investigative sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

6.4.5 Reporting to Hospital Risk Management:

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

7. CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from study when any of following criteria occur: new invasive cancer diagnosis or recurrence; decision of the participant to stop receiving chemotherapy treatment; request of the patient to withdraw; illness that prevents further administration of the intervention; or study team or treating clinicians deem continued participation not safe for patient. Patients who are removed from study will be asked to complete follow-up assessments if clinically feasible and patients are agreeable. Reason for removal from study will be recorded in patient's study record.

8. DATA REPORTING / REGULATORY REQUIREMENTS

The Kaiser Permanente of Northern California study team will oversee all adverse events with a designated Data and Safety Monitoring Board. This board will include Dennis Black (biostatistician), Kerri Winters Stone (exercise interventionist), Kathleen Van Loon (gastro oncologist) and study liaison.

9. STATISTICAL CONSIDERATIONS

9.1 Study design:

This randomized controlled trial of resistance training intervention in colon cancer patients receiving chemotherapy consists of two arms: an in-person and telephone-based intervention to promote home-based resistance training, and a wait-list, control group. After consent and baseline visit measurements, randomization assignment will utilize a covariate adaptive randomization procedure which ensures that equal numbers of patients are assigned to each study arm and that the two arms remain balanced on five key characteristics: site of participation [Kaiser Permanente vs Penn State vs Dana-Farber]; gender [male vs female]; cancer stage [stage II vs stage III], and duration of chemotherapy [3 months vs 6 months]; planned chemotherapy regimen [FOLFOX vs CAPOX vs capecitabine vs 5-FU/LV]. This randomization method (also known as the minimization method) has been demonstrated to outperform simple randomization or stratified randomization in terms of achieving balanced groups, particularly in smaller trials with multiple important prognostic factors.

The primary objective of this trial is to compare the effect of a RT intervention versus a wait-list control on chemotherapy dose reductions, dose delays, early discontinuation of chemotherapy and treatment-related toxicity. The secondary objective is to compare the effect of the intervention versus wait-list control on changes in inflammatory biomarkers, and the tertiary objective is to compare pre and post intervention pharmacokinetics of 5-FU and oxaliplatin. The d3 Creatine objective is to compare the effect of a RT intervention versus a wait-list control on d3 creatine muscle mass at 6 months.

9.2 Sample size, accrual time and study duration:

One hundred and eighty (180) participants will be recruited and randomized over a total of 3.5 years. Patient involvement and data collection will last approximately 6 months.

9.2.1 From Section D. Study overview of the original KPNC application approved 2017

3. How many participants will be enrolled in this study, or how many electronic records or medical records will be used? Provide your best estimate if you are not sure

Number of KPNC participants or records:	Approximately 115 participants to be enrolled
Records used:	Approximately 7500-KPNC records used
Number of non-KPNC participants or records:	Approximately 65 participants enrolled
Total number of participants or records:	Approximately 180* participants enrolled **Due to the impact of the COVID-19 pandemic on the study, we estimate that the total number of participants will be within the range of 10% above the original total of 180 participants*

9.3 Statistical analysis:

9.3.1 Primary endpoints:

All data analyses will be by intent-to-treat, though in exploratory analyses we will consider compliance to intervention (defined as ≥75% of planned sessions) and changes in MM. We will use multiple linear regressions to assess the difference between the intervention and wait-list control groups in mean relative dose intensity (RDI) for each agent and in mean average RDI (ARDI) across all agents. Continuous model covariates will be categorized either as quartiles or into clinically relevant categories (e.g. WHO BMI classification).

Analysis of number of grade 3 and 4 toxicities in relation to randomization arm will utilize Poisson regression given that this outcome can be characterized as a count. These regression models will provide point and interval estimates of adjusted proportional differences in rates of toxicities (expressed as rate ratios) between the control and intervention groups.

9.3.2 Secondary endpoints:

Analyses of inflammatory markers in relation to baseline body composition will utilize multiple linear regression techniques These analyses of associations at baseline will be conducted in each randomization arm separately, followed by an analysis in the full sample (differences in associations at baseline across arms are not expected).

Pharmacokinetics: As 5-FU is known to undergo nonlinear disposition, compartmental modeling will be conducted using nonlinear mixed effects analysis with NONMEM (Icon Development Solutions, Hanover MD). NONMEM allows for simultaneous estimation of fixed-effects values (e.g. CL and V) and random-effects values (e.g. inter-individual, inter-occasional, and residual unexplained variability). Previous models of 5-FU and oxaliplatin[28] have been reported and will serve as a basis for development of the structural model. The final structural (e.g. 1- vs. 2-compartment) and error models (e.g. additive or proportional) will be chosen based on minimization of the objective function value (OFV, -2 log likelihood) and evaluation of diagnostic plots generated in R. During the covariate selection process, various measures of body composition (e.g.MM, MM/FM ratio) will be compared to identify the contribution of these parameters to PK variability in colon cancer patients. Pre- and post-intervention PK parameters (e.g. CL, V) will be compared using a paired t-test.

9.3.3 d3 creatine endpoints:

We will first assess the distribution of the baseline covariates by FORCE randomization arm. Most outcomes will be treated as continuous variables and we will fit linear regression models (e.g., for the continuous outcomes such as change in d3 creatine muscle mass, SPPB and SF-36 score, grip strength, relative dose intensity, and values of inflammatory markers, CEA and cardiometabolic risk factors). We will assess departures from regression model assumptions primarily by diagnostic plots of residuals, with attention to detection of non-constant variance of errors and detection of outliers that may indicate the need for a variance stabilizing transformation of the dependent variable. In secondary analyses, when considering outcomes dichotomously, we will fit logistic regression models (e.g., for abnormal CEA values).

Aim 1 is a randomized comparison of the FORCE resistance training intervention to the waitlist control. Analyses in Aims 2-4, however, are subject to confounding. Our *a priori*

set of potential confounders for cross-sectional analyses at baseline includes age, sex, body mass index or weight, race/ethnicity and tumor stage. For longitudinal analyses, potential confounders also include chemotherapy type, intervention assignment and time from surgery and/or chemotherapy start to assessment. We will include those covariates resulting in a 10% or more change in the d3 creatine muscle mass regression coefficient. The change-in-estimate approach to confounder selection performs well with regard to power, bias, mean squared error and confidence interval coverage.

9.3.4 Power:

Given previous exercise studies in cancer patients, we assume approximately 10% drop out with no follow-up DXA and blood draw for biomarker assessment. We expect chemotoxicity metrics (RDI, # toxicities) to be assessed on the full sample. We have sufficient power (.80) to detect a between arm difference in means of at least .42 standard deviation (s.d.) units (two-sided t-test, α=.05) in Aim 1 analyses of chemotoxicity. With an expected RDI s.d. of 17.3[45]**,** the minimum detectable difference in mean RDI is 7.3%, which is clinically meaningful and similar to effects found with a study of exercise among breast cancer patients receiving adjuvant chemotherapy[45]. With the expected loss to follow-up and reduced sample size of 81 per group, the minimum detectable between arm difference in mean change is .44 units, which is considered in the "small" to "medium" range in effect size using the terminology and classification of Cohen. Relevant to Aim 4, on pharmacokinetics, a sample size of 30 subjects will provide sufficient power (.80) to detect a mean change of at least 0.5 s.d. units (two-sided t-test, α=.05). Given previous data[26], the minimum detectable change in clearance of oxaliplatin or 5-FU due to RT is 15%.

10. STUDY INVESTIGATORS

The study's Principal Investigators include:

- Bette Caan, DrPH, Kaiser Permanente, Division of Research
- Jeffrey Meyerhardt, MD, MPH, Dana-Farber Cancer Institute
- Kathryn Schmitz. PhD, Penn State Cancer Institute

Co-Investigators include:

- Justin Brown, PhD, Pennington Biomedical Research Center, Louisiana State University
- Kristin Campbell, PT, MSc, PhD, University of British Columbia
- Elizabeth Feliciano, Kaiser Permanente, Division of Research
- Raymond Liu, MD, The Permanente Medical Group
- Charles Quesenberry, PhD, Kaiser Permanente, Division of Research
- Sara Quinney, PhD, Indiana University
- Renate Winkels, PhD, Penn State Cancer Institute

11. DATA PRIVACY AND SECURITY

Disclosure of PHI to non-KPNC workforce

PHI will be disclosed to members of the Data Safety and Monitoring Board (DSMB) as well as an independent contractor, Dr. Barbara Sternfeld. The DSMB members will oversee and monitor the study to ensure participant safety and the validity and integrity of the data. Dr. Sternfeld will act as exercise intervention liaison, including overseeing exercise sessions, case review with trainer, and contact with DSMB. Types of PHI that will be disclosed include dates.

Disclosure of deidentified datasets to non-KPNC workforce
The following investigators and research staff from collaborating institutions will receive deidentified datasets (i.e., contains no PHI identifiers):

- Jeffrey Meyerhardt, MD, MPH, Dana Farber Cancer Institute
- Kathryn H. Schmitz, PhD, MPH, FACSM, FTOS, The Pennsylvania State University, Hershey Medical Center
- Kristin Campbell, BSc PT, PhD, University of British Columbia
- Justin Brown, PhD, Pennington Biomedical Research Center, Louisiana State University
- Sara Quinney, PhD, Pharm. D., Indiana University
- Barbara Sternfeld, PhD, independent contractor, Kensington, CA

Deidentified datasets will include intervention data such as exercise adherence; study measure and questionnaire data from baseline and follow-up data collection; chemotherapy data and demographic data.

Data transfer
All data will be shared securely with investigators and staff via KPNC secure file transfer.

Data storage
All study data including data with PHI will be stored electronically on a secure, password protected KP server behind a firewall and in an online, secure, password protected REDCap database. Only approved research study staff have REDCap access. REDCap data will be archived off the server within 12 months after data collection ends. No PHI data will be stored for any part of the study on an endpoint computing device or removeable media (i.e., workstation, laptop, flash drive, CD).

Blood biospecimen samples will be stored at Kaiser Permanente Northern California and Dana Farber Cancer Institute. Samples will be kept until they are used up for future studies or the Principal Investigators decide to destroy them.

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13. APPENDIX

13.1 Recruitment Communications
- **13.1.1** Email to Oncology Provider
- **13.1.2** DFCI Recruitment Letter
- **13.1.3** Recruitment Phone Script
- **13.1.4** Recruitment Email/Letter to Participant

13.2 Phone Screening Forms and Questionnaires
- **13.2.1** Screening Eligibility Form
- **13.2.2** Physical Activity Readiness Questionnaire (PAR-Q)
- **13.2.3** Physical Activity Screening Questions
- **12.2.4** Additional Screening Questions
- **13.2.5** Participant Information Form
- **13.2.6** COVID-19 Phone Script- Staff Screening of In Person Visits

13.3 Consent Form
- **13.3.1** Consent Form
- **13.3.2** eConsent and HIPPA Authorization Forms
- **13.3.3** REDCap eConsent and HIPPA Signature Sections
- **13.3.4** FORCE Invite and eConsent REDCap Email

13.4 Baseline and Post-Intervention Questionnaires
- **13.4.1** Demographic Information
- **13.4.2** Medical Outcomes Study 36-Item Short Form (SF-36)
- **13.4.3** Intervention Follow-up Survey

13.5 Physical Activity Assessments and Exercise Intervention Materials
- **13.5.1** Abbreviated Paffenbarger Physical Activity Questionnaire
- **13.5.2** Physical Function Tests Protocol and Assessment Sheets
- **13.5.3** Exercise Protocol
- **13.5.4** Participant Exercise Log
- **13.5.5** Exercise Trainer Phone Call/Clinic Visit Questions

13.6 Nutrition Assessments and Intervention Materials
- **13.6.1** Food Frequency Questionnaire (FFQ) Block 2014
- **13.6.2** Nutrition Protocol
- **13.6.3** Participant Protein Log
- **12.6.4** Usual Care Protein Handout

13.7 Chemotherapy Toxicity, Side Effects, and Injury History Forms and Email
- **13.7.1** Patient-completed NCI- PRO-CTCAE
- **13.7.2** Email regarding NCI-PRO-CTCAE
- **13.7.3** Patient-completed Side Effect Questionnaire
- **13.7.4** Chemotherapy Treatment Form
- **13.7.5** Chemotherapy-associated Toxicity Form
- **13.7.6** Injury History Form

13.8 Anthropometric Measurements and Blood Draw Procedures
- **13.8.1** Waist and Hip Circumference, Height and Weight
- **13.8.2** Dual X-Ray Absorptiometry Protocol
- **13.8.3** D3 Creatine Dilution Protocol
- **13.8.4** Blood Draw and DXA Instruction Cards
- **13.8.5** DXA Cover Sheets
- **13.8.6** KP PK Blood Draw Protocol

13.9 Usual Care Handout

13.10 Thank You Card Text