UNIVERSITY OF ROCHESTER MEDICAL CENTER

WILMOT CANCER INSTITUTE

A mobile health exercise intervention for older patients with myeloid neoplasms

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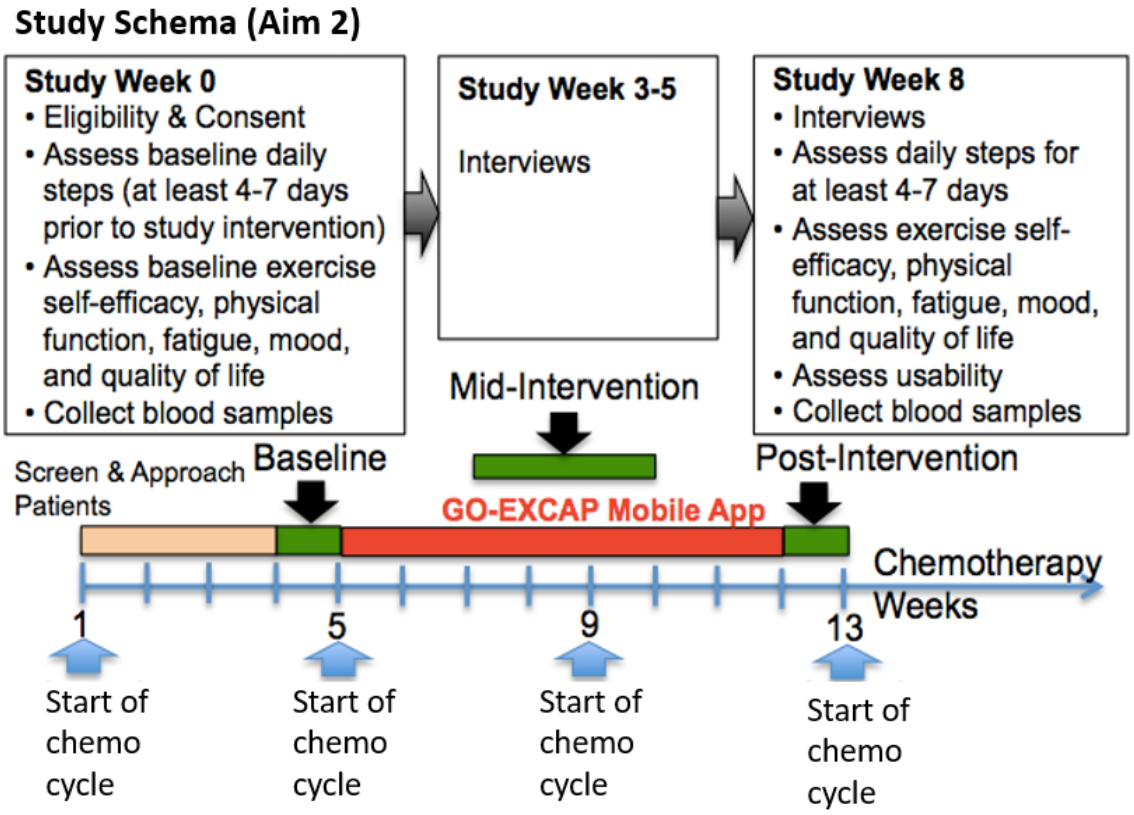
Study Schema (Aim 2)



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1.0. Background

1.1. Myeloid neoplasms are diseases of aging

MN are a group of diseases that include acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), MDS/myeloproliferative neoplasm (MPN) overlap, chronic myelomonocytic leukemia (CMML), and atypical chronic myeloid leukemia (aCML).[1] Over 60% of MN are diagnosed in adults aged ≥60 years.[2,3] For fit older patients with AML (i.e., without significant comorbidities or disabilities), the standard first-line treatment consists of intensive inpatient chemotherapy. Intensive chemotherapy provides the best chance for durable remission, but it is associated with a high treatment-related mortality (60-day mortality: 15-20%).[4,5] Intensive therapy is utilized in <1% of older patients with AML seen in the community oncology setting, due to various reasons such as distance to tertiary centers and need for hospitalizations.[6] In the last decade, low-intensity outpatient treatments with reduced treatment-related mortality rates, such as hypomethylating agents (HMA), have become available.[7–9] These treatments have permitted more older patients with AML, including those with comorbidities and disabilities, to receive leukemia-directed therapy.[10] Furthermore, given the recent FDA approval of HMA combination therapy for AML (e.g., HMA and venetoclax), which has similar or better efficacy than intensive therapy,[11] HMA-based therapies will be used more widely in older patients with AML. For older patients with other MN requiring chemotherapy, HMA are often the treatment of choice.[12] Thus, HMA are now standard of care for older patients with MN. HMA are typically given continuously until progression, death, or stem cell transplant.

1.2. Even with HMA, a high percentage of older patients with MN experience physical function decline and symptoms (e.g., fatigue, mood disturbances).

In prior studies, up to 98% of older patients with MN receiving intensive chemotherapy experience physical function decline and symptoms.[13–15] Our group and others have also shown that 73% of older patients with MN receiving HMA had impairments in physical function and 33% reported mood disturbances.[16,17] Physical function decline and symptoms can lead to reduced quality of life (QoL), treatment interruptions, and shorter survival.[13,18–22] Therefore, it is imperative to develop interventions for older patients receiving HMA that prevent physical function decline and improve symptoms so that they can maintain their QoL and continue to receive cancer treatments.

1.3. Older patients with MN can exercise and may derive benefits from exercise.

Exercise may prevent physical function decline and improve symptoms.[23–26] Older adults can derive benefits from exercise even if they only maintain or minimally improve physical activity from baseline.[27] A previous systematic review has shown that exercise is safe in frail older adults.[28] Three pilot studies evaluated exercise in 50 older patients with MN (only one receiving HMA was included) and showed that they can exercise and that it was safe. In addition, exercise improved physical function, fatigue, mood disturbances, and QoL.[29–31] In our own pilot work, older patients with MN receiving HMA reported

walking at least an average of 2k-3k steps/day, which is comparable to prior exercise studies in older patients with solid tumors, suggesting that they have similar exercise capacity. Overall, our pilot data and prior studies suggest that older patients with MN can exercise safely and may benefit from it, but exercise interventions tailored to this population are limited.[32]

1.4. Exercise for Cancer Patients (EXCAP):

Dr. Mustian (co-investigators) developed EXCAP, an individually tailored, low- to moderate-intensity, home-based walking and progressive resistance exercise program designed for patients with cancer and delivered by an exercise physiologist. By design, EXCAP is tailored to the physical capacity of patients with cancer. Our data from >300 older patients undergoing active cancer treatments from 4 phase 2/3 studies demonstrated that they were able to perform the walking (average steps walked/day=4k-11k at post-intervention) and resistance exercises (15-22 min/day, 2-4 days/week).[23,27,33,34] EXCAP also improved physical function, fatigue, and mood in patients with solid tumors.[35–37] In older patients with solid tumors, we have shown that EXCAP improved physical function (measured using the Short Physical Performance Battery, SPPB), mood, and QoL, but effect sizes were small (Cohen's d=0.10-0.30).[23,27,38] Older patients had lower exercise adherence than their younger counterparts (average steps walked/day=4k vs. 5k at post-intervention).

1.5. The use of a mobile health (mHealth) application (app) may improve exercise adherence in older patients with MN.

Exercise adherence can be a challenge in older patients with MN due to comorbidities, symptoms, lack of exercise self-efficacy, and limited access to exercise oncology professionals and facilities.[39–42] mHealth has the potential to improve exercise adherence by enhancing exercise self-efficacy and by helping to address barriers to exercise in real time.[43,44] In our systematic review of studies in the cancer population, however, we found that older patients with MN are rarely included in mHealth exercise studies.[43]

1.6. PointClick Care Mobile App:

We have worked with a mHealth company (PointClickCare, formerly TouchStream) to upgrade an app (TouchStream) for monitoring older patients (12 had MN) receiving cancer treatment.[16] Our pilot data suggest that the app is usable and feasible (Table 1). I conducted interviews with 16 patients to elicit barriers and facilitators for adaptation of the app and revision of the study protocol. Patients indicated their willingness to exercise and preferred a structured exercise program in combination with the app over physicians' recommendations to exercise without a structured program and app.

1.7. Several mechanisms are associated with physical function decline, fatigue, and mood disturbances.

Potential mechanisms include inflammatory dysregulation, neuroimmunological changes, energy imbalance, and skeletal muscle changes (e.g., mitochondrial dysfunction, decline in neural function, reduced satellite cell function, defects in calcium homeostasis);[45,46] these are often inter-related.[47,48] Inflammatory dysregulation, in particular, has strong mechanistic evidence because of its association with frailty in older adults[49,50] and because it can affect virtually every biological system (the most relevant are the muscular, cardiovascular, and cerebrovascular systems).[45]

1.8. Tumor necrosis factor (TNF)α and related inflammatory cytokines are associated with physical function decline, fatigue, mood disturbances, and worsening QoL in older patients with MN.

TNFα is involved in early inflammatory responses and is regarded as the "master regulator" of inflammation.[51,52] Preclinical studies demonstrate that cancer and chemotherapy increase serum TNFα and related cytokine levels [e.g., interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8)].[53–55,56(p),57] Activation of TNFα and related cytokine pathways leads to physical function decline, fatigue, and mood disturbances,[58–62] which are abrogated by inhibition of these pathways.[62,63] In older adults with MN, we have shown that higher baseline serum TNFα levels were associated with shorter survival. In patients with MN, our group and others also found that increased serum TNFα, soluble TNF receptor 1 (sTNFR1), and related cytokine levels were associated with physical function decline, fatigue, mood disturbances, and worsening QoL.[64–66] Exercise reduces inflammation, which may explain how exercise prevents physical function decline and improves fatigue and mood disturbances.[67,68]

1.9. Understanding exercise-induced changes in the TNFα and related cytokine pathways may help to tailor exercise prescriptions for older patients with cancer in clinical practice.

In patients with higher serum TNFα levels, a lower dose of exercise may be sufficient to decrease serum TNFα levels and prevent physical function decline. However, the epigenetic regulation of TNFα in the context of exercise is not well characterized. DNA methylation is an epigenetic mechanism that can be stably inherited throughout cell divisions.[69] DNA methylation is the addition of methyl groups to the DNA molecule at the CpG sites where a cytosine nucleotide is followed by a guanine.[70] DNA methylation of the *TNFα* gene promoter region decreases *TNFα* gene and protein expression.[71,72] Prior studies have shown that exercise increases *TNFα* gene promoter methylation and decreases *TNFα* gene and protein expression.[73–76] A better understanding of the TNF*α* and related cytokine pathways can identify biomarkers to help tailor exercise prescriptions.

To summarize, we chose the TNFα pathway as our translational focus because 1) our preliminary data showed that higher serum TNFα and soluble TNF receptor 1 levels were associated with physical function decline, mood disturbances, and shorter survival;[64] 2) exercise increases *TNFα* gene promoter methylation and decreases *TNFα* gene and protein expression;[73–76] 3) it will allow us to expand our preliminary data and explore other TNFα related cytokine pathways (e.g., IL-1β, IL-6, IL-8); and 4) we have the

expertise to reliably measure, analyze, and interpret *TNFα* gene promoter methylation and *TNFα* gene and protein expression in a clinical trial.[77] While we focus on older patients with MN, this population serves as a model for studying an individually tailored mHealth exercise intervention among vulnerable older patients receiving prolonged cancer treatments to prevent physical function decline and improve symptoms. Findings from our studies will inform research and practice for a large proportion of older patients who are currently understudied in behavioral intervention trials. This work is also highly novel and may lay the foundation for the use of biomarkers in the design of behavioral interventions to improve outcomes in older patients with cancer.

Summary of knowledge/Proposed Solution:
No mHealth exercise intervention is currently available for older patients with MN receiving outpatient chemotherapy, specifically HMA. TNFα and related cytokines are associated with physical function decline, fatigue, and mood disturbances. Based on our expertise and prior studies, we propose to integrate the content of EXCAP into the PointClick Care app to enhance older patients' adherence to exercise and to understand exercise-induced changes in physical function, fatigue, mood, QoL, and TNFα and related cytokine pathways.

The mobile app and EXCAP have been studied individually in previous studies.[16,23,33,34,78] In this study, we plan to combine them for older patients with MN receiving outpatient chemotherapy including HMA.

2.0. Aim and Hypothesis

2.1. Primary Aim

To develop a mobile app delivery platform integrating EXCAP and adapt its content, format, and delivery for older patients with MN receiving HMA using feedback from 15 patients.

2.2. Secondary Aim

To assess the feasibility of a mobile health exercise intervention (GO-EXCAP Mobile App) over 8± 4 weeks in a single-arm pilot study in 25 patients with myeloid neoplasms receiving outpatient chemotherapy (including HMA).

2.3. Exploratory Aim

To examine relationships among *TNFα* and related cytokine gene promoter methylation and gene and protein expression.

2.2.1. Hypothesis

The GO-EXCAP Mobile App will be feasible in older patients with myeloid neoplasms receiving outpatient chemotherapy.

2.2.1. Feasibility metrics

The feasibility of the GO-EXCAP Mobile App will be evaluated based on the following:

a) Percentage of patients wearing the activity tracker and entering resistance exercise data into the mobile app.
b) Percentage of patients performing both walking and resistance exercises during the study period days.
c) Recruitment rates (percentage of patients who are approached and agree to enroll).
d) Retention rates (percentage of patients who are enrolled and complete post-intervention assessments).

3.0. Study Design and Population

3.1. Study Settings
Wilmot Cancer Institute (WCI), University of Rochester Medical Center (including WCI-affiliated community practices such as Interlakes Oncology, Dansville, Pluta, Olean, Wellsville)

3.2. Study Type
Aim 1: Qualitative study

Aim 2: Single-arm pilot study

3.3. Study Population
Aim 1: We will obtain feedback from 15 older patients receiving HMA. Our planned sample size (N=15) will allow us to achieve thematic saturation.[79,80] To obtain 15 patients, we will consent up to 20 patients to account for screen fail or withdrawal.

Aim 2: We will recruit 25 older patients receiving outpatient chemotherapy (see Section 8.2.2 for sample size justification). To obtain 25 patients, we will consent up to 45 patients to account for screen fail or withdrawal.

3.4. Inclusion and Exclusion Criteria

Inclusion criteria
- Age ≥60 years (conventional definition of older age in clinical trials of MN)[81–83]
- Have a diagnosis of MN
- Receiving outpatient chemotherapy (e.g., HMA)
- English speaking
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
- No medical contraindications for exercise per oncologist
- Able to walk 4 meters as part of Short Physical Performance Battery measured walk (with or without assistive device)
- Able to provide informed consent

Exclusion criteria
- Platelet count of 10,000 per microliter or less in the most recent blood draw (due to risk of spontaneous bleeding) prior to transfusion (i.e., patients are allowed to enroll if their platelet count is 10,000 per microliter or less but is scheduled to receive transfusion the day of consent)

Each subject's eligibility will be documented on redcap. This will be printed and signed and dated by the principal investigator.

3.5. Number of Subjects

Aim 1: We plan to enroll 15 patients in 3 months. In any given week, between 10 and 20 older patients with MN are receiving HMA at the Wilmot Cancer Institute. In a previous qualitative study conducted in this population, recruitment rate was close to 100%.[84] Therefore, we expect to be able to recruit 15 patients in 3 months.

Aim 2: Annually from 2012-2017, four oncologists saw approximately 150 patients with MN aged ≥60 at the Wilmot Cancer Institute, and 70% received outpatient HMA. In prior studies of older patients (including MN) enrolled on behavioral pilot intervention studies at our institution, the recruitment rate was 65-75%.[85,86] Therefore, we expect to be able to recruit 25 patients in 18 months.

3.6. Gender of Subjects

The gender ratio of patients to be enrolled on the study will be similar to the gender ratio of myeloid neoplasms in older adults (approximately 1.2:1 Male to female ratio).[87]

3.7. Age of Subjects

We will recruit patients with myeloid neoplasms aged 60 and above (from date of consent, confirmed on electronic medical record).

3.8. Racial and Ethnic Origin

Myeloid neoplams affects all races with similar rates. Whites, African American and Hispanics make up approximately 65%, 30% and 5%, respectively, of the older population in Rochester, New York.[88] As we limited enrollment to English-speaking patients, we anticipate a higher percentage of whites in our study. The study has no enrollment restrictions based upon race or ethnic origin.

3.9. Vulnerable Subjects

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

4.0. Recruitment and Consent

Subjects will be enrolled at the University of Rochester Medical Center (URMC) Wilmot Cancer Center and WCI-affiliated community practices such as Interlakes Oncology, Dansville, Pluta, Olean, Wellsville. Study subjects will be recruited from the malignant hematology clinics at WCI and general oncology clinics at WCI-affiliated community practices. We plan to enroll 40 subjects (15 in phase 1 and 25 in phase 2) over a course of 2 years.

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.

4.1. Identification of Study Subjects, Recruitment, and Consent Procedures

Study subjects will be identified in multiple ways. First, patients will be identified by their treating physician, the nurses that work with the physicians, and the study coordinator. The study coordinator will work closely with the physicians and nurses to identify those patients that are anticipated or have begun treatment with chemotherapy. Second, with permission from oncology providers, we will screen for eligible patients from clinic schedules. The study coordinator contacts the physician (or their designee) and informs them that a patient may be eligible for the study. The physician (or their designee) then confirms if the patient is a study candidate or not (including whether they are a candidate to exercise). This will be documented in the subject research chart. If there is a question about eligibility, the principal investigator will be contacted and will meet with the patient, review the medical records, and perform an assessment of eligibility if necessary. The same identification process will be used for all sites.

For **in-person consent,** below are the possible scenarios for obtaining consent.

1) Physician/Study Investigator makes the initial contact andprovides consent form, and patient signs consent with the physician on the same day: After confirming with the physician (or their designee) that a patient is a potential candidate for the study, the study staff will provide a consent form to the treating physician/study investigator so he/she can provide it to the patient during an in-person clinic visit. The physician/study investigator will go over every detail of the study during the clinic visit with patient. If agrees, the patient will sign the consent form with the physician/study investigator during the same in-person visit.

2) Study staff makes the initial contact and provides consent form, and patient signs consent with the study staff on the same day:

After confirming with the physician (or their designee) that a patient is a potential candidate for the study, the patient will be provided with an informed consent form by the study staff when they come in for an in-person clinic visit. The study staff will introduce the study to the patients and go over every detail of the study. If agrees, the patient will sign the consent form with the study staff during the same in- person visit with the study staff.

For **verbal consent,** below are the possible scenarios for obtaining consent. Generally two in-person visits are required prior to the start of intervention (the first in-person visit is to provide the wearable tracker and actigraphy, the second in-person visit to perform the in-person assessments and provide the tablet). By allowing verbal consent, we will be able to mail the wearable tracker and actigraphy to the patient.

1) Physician/Study Investigator makes the initial contact, study staff follows up with the patient on the phone, and patient provides verbal consent on the phone: After confirming with the physician (or their designee) that a patient is a potential candidate for the study, the physician/study investigator confirms with the patient that he/she is willing to speak with the study staff about the study. The study staff will then call the patient via phone. The study coordinator will use the verbal consent script as a written aid and will go over every detail of the study with the patient to recruit them for the study. Study staff will sign and date it to confirm that he/she followed the script and the patient agrees to participate in the study. An information sheet summarizing the study and patient' s involvement will be mailed /emailed to the patient for their records.

2) Physician/Study Investigator makes the initial contact and provides consent form, study staff follows up with the patient on the phone, and patient provides verbal consent on the phone: After confirming with the physician (or their designee) that a patient is a potential candidate for the study, the study staff will provide a consent form to the treating physician/study investigator so he/she can provide it to the patient during an in-person clinic visit. If the patient is interested but does not want to consent on the same day, the patient will bring the consent form home. The study staff will then call the patient via phone. The study coordinator will use the verbal consent script as a written aid and will go over every detail of the study with the patient to recruit them for the study. Study staff will sign and date it to confirm that he/she followed the script and the patient agrees to participate in the study. An information sheet summarizing the study and patient's involvement will be mailed/emailed to the patient for their records.

3) Study staff makes the initial contact and provides consent form, study staff follows up with the patient on the phone, and patient provides verbal consent on the phone: After confirming with the physician (or their designee) that a patient is willing to speak with the study coordinator about the study, the patient will be provided with an informed consent form by the study staff when they come in for an in-person clinic visit. If the patient is interested but does not want to consent on the same day, the patient will bring the consent form home. The study staff will then call the patient via phone. The study coordinator will use the verbal consent script as a written aid and will go over every detail of the study with the patient to recruit them for the study. Study staff will sign and date it to confirm that he/she followed the script and the patient agrees to participate in the study. An information sheet summarizing the study and patient's involvement will be mailed/emailed to the patient for their records.

4.1.1. Informed Consent

Informed consent will be obtained from the patient by the study investigators or coordinators. Consent documents will be signed by the patient and maintained in the patient record with copies provided to the patient. For verbal consent, documents will be maintained in the patient record with copies provided to the patient.

4.1.2. Baseline Measures and Study Procedures

After consent, the patient will complete baseline measures. Study coordinator will be available to assist the patient. The study coordinator will obtain information necessary to complete the forms capturing clinical data from the patient's medical records when the patient is unable to provide this information in sufficient detail (e.g. type of myeloid neoplasms, antecedent hematologic malignancies, treatment regimen).

For patients consented at Olean, Wellsville, and Dansville, they will be asked to meet with the study coordinator at the Wilmot Cancer Institute/Strong Memorial Hospital to conduct research activities. No research activities will be conducted at these sites.

4.1.3. Human Subject Protection

Ethical standards for human subjects will be strictly followed in accordance with the University of Rochester Research Subject Review Board Investigator Guidance policy.[89]

4.1.4. Participation

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.

4.1.5. Duration

Aim 1: The qualitative portion of the study will involve one semi-structured interview. Interviews with the patients will be held in person in a private space (clinic or office space). Interviews will be audio-recorded and led by study investigators and will last 30 minutes. These recordings will be uploaded to Box, and the recordings will be deleted from the audio-recorder.

Aim 2: Study participants will be consented to actively participate, receive phone calls or meet with the research study team at the baseline visit (week 0) and 8± 4 weeks after the intervention (week 8± 4). The research team may contact participants in the future to gain further information first hand regarding patients' overall health and treatment, the study team may decide to take participants off the study without their consent if the study is stopped. Additionally, study participant data will be kept for 7 years at URMC, even after the study is closed or a study participant passes away. It will be maintained in a locked database with password access only (See Section 9).

5.0. Registration

5.1. To register a participant who meets the eligibility criteria and who has signed the informed consent document, study staff will log on to OnCore and enter the information outlined in section 5.2 below.

5.2. Information Requested at Registration

- 5.2.1 Site
- 5.2.2 Most recent IRB approval date
- 5.2.3 Eligibility verification
- 5.2.4 Verification that consent form has been signed and who signed by (patient and/or health care proxy) and date signed
- 5.2.5 Treatment facility (Wilmot Cancer Center)
- 5.2.6 Participant's identification
  - 5.2.6.a First and last names
  - 5.2.6.b Birth date (MM/DD/STREAM)
  - 5.2.6.c Gender
  - 5.2.6.d Race
  - 5.2.6.e Five-digit zip code
  - 5.2.6.f Medical Record Number
  - 5.2.6.g Ethnicity
  - 5.2.6.h Patient's preferred and alternate phone numbers
  - 5.2.6.i Date of baseline Visit

5.3. Initial Assessment

After consent procedures are completed, the patient, with the help of the study coordinator, will complete a baseline assessment (see Section 7.2). Patients who are eligible will be enrolled and complete study procedures. For Aim 1, this will involve one semi-structured interview. For Aim 2, patients will be provided with the intervention and will be asked to complete post-intervention assessment at week 8 (± 4 weeks).

6.0. Intervention

6.1. EXCAP Exercise Program

The first component of the EXCAP exercise program is an individually tailored walking prescription and provides low to moderately intense aerobic exercise (3-5 exercise rating of perceived exertion on the American College of Sports Medicine [ACSM] revised rating scale, which is a visual analog scale ranging from 1 = “Not tired at all” to 10 = ”So tired, I can’t go anymore”) 7 days a week. This walking prescription will be developed and individually tailored for each subject according to step data reported on the web portal. A Garmin activity tracker, a wearable sensor-based device, will be used record the number of steps they walk daily during the 4-7 days baseline assessment and then with the help of an exercise physiologist to calculate the average number of steps they walk daily during that period. The wearable devices will be registered by the research team (no phone or mobile identification numbers will be stored with data, and no GPS data will be collected to identify locations). Using the baseline average number of steps walked daily, patients are encouraged to increase their total steps walked by a minimum of 5% per week, while maintaining a moderate intensity. Subjects are encouraged to reach the ACSM suggested 10,000 steps a day if possible (this is not mandatory). As an instructional and motivational tool, at the start of the exercise intervention, a table will be provided that includes the average number of steps walked at baseline, as well as, the number of steps that would represent increases of 5%, 10%, 15%, and 20% over this baseline amount for each of the 8 weeks of the intervention period

The second component of the exercise program is an individually tailored therapeutic resistance band exercise prescription designed to provide low to moderately intense progressive resistance exercise [3-5 exercise rating of perceived exertion (RPE) on the ACSM revised rating scale] 7 days a week. Subjects are given a set of 3 color-coded therapeutic resistance bands representing varying levels of resistance. The exercise physiologist will explain the proper use of the resistance bands, safety, and the appropriate mechanics for performing the resistance training exercises. Subjects are instructed to begin with an individually determined number of sets (1 set = 8-15 repetitions) for each of the sixteen exercises at a moderately challenging level (RPE=3-5) 7 days a week. The exercises target the upper and lower body. The exercise physiologist will work with the subject to find an optimally challenging number of sets and repetitions with the appropriately colored resistance band for each exercise with each patient. Subjects are instructed to increase the intensity by changing to a different color band or by shortening the initial length of the band for increased resistance. They are encouraged to progressively increase from their individual baseline sets and repetitions to a maximum of 4 sets of 15 repetitions for each exercise daily over the course of the 8-week (± 4 weeks) intervention at a rate that is optimally challenging. The therapeutic resistance band exercise prescription will be developed and individually tailored for each subject by the exercise physiologist. Each subject will report the intensity of their resistance exercise using 1) the rated perceive exertion (RPE) scale and 2) time spent for resistance band exercise by entering these data directly on the tablet.

6.2. PointClick Care Mobile App

PointClick Care is a mobile app that is preloaded on a tablet. The app was initially designed with the goal of helping people live independently. The app provides assistance in managing medications, chronic health conditions, doctor appointments, and activities of daily living including reminders to exercise. The PointClick Care app is connected to a data plan (which will be paid for by the study) for internet access, as well as a web portal that is accessible using a desktop or laptop computer of which internet access is required. The University of Rochester IT department has been contacted. As per the University policy for devices, the hard drive must be encrypted to protect any patient data. PointClick Care encrypts all PointClick Care data transferred between backend servers and the tablets. Communications to the server is validated by signed trusted server certificate. Data at rest is always encrypted. PointClick Care caches data on the tablet, and stores data on a PointClick Care server. On the tablet the cache in encrypted, the backend server hosts a Microsoft SQL Server database. The volume used by SQL Server is encrypted. Only the PointClick Care app, with a valid authentication key, can read this data. PointClick Care has a means to disable the PointClick Care app on a tablet. This feature only works, however, if the Tablet is connected to the server.

6.2.1 Tablet Device

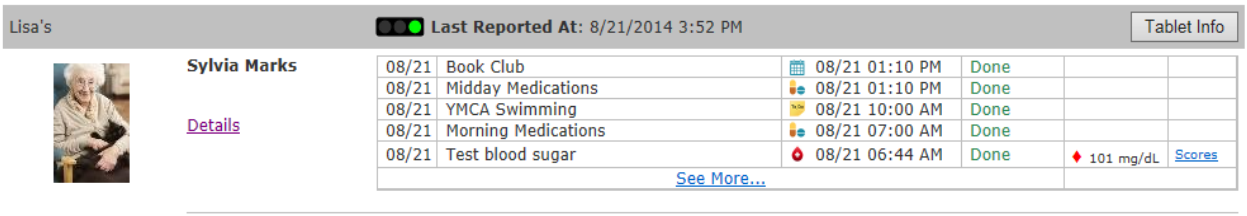
The tablet device contains the PointClick Care app. The default screen displays the schedule for the day including doctor appointments, to-do-list and reminders (such as taking medications, or exercising) (Figure 2). Activities displayed on the tablet can only be entered through the web portal (i.e. have you walked at least 4000 steps today?). Users can select whether the tasks are completed on the tablet and they can manually enter the number of daily steps. The system also allows the user to create questionnaires.

Figure 2: Default screen of the PointClick Care application

6.2.2. Web-Portal

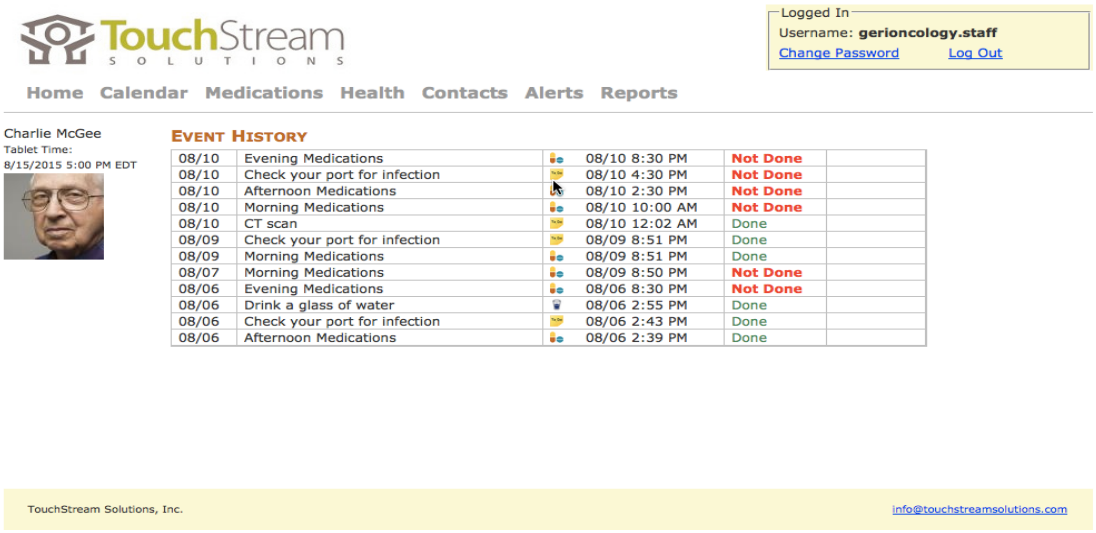
The web portal is accessed through a web address (https://client.PointClick Caresolutions.com) using a computer by the investigators and exercise physiologist and/or patients if they wish. The homepage displays the patient's information and a list of activities followed by the date and time, and whether the tasks have been completed (Figures 3 and 4). This function will allow the exercise physiologist to monitor for exercise adherence at a distance.

Figure 3: Homepage of the web-portal



User can access the profile by clicking "see more…" or "details". There are several functions on the web portal (Figure 3). The toolbar includes "home", "calendar", "medications", "health", "contacts", "alerts" and "reports". Under "calendar" tab, activities can be entered as events (e.g. have you walked at least 4000 steps today). Events can be entered as single or recurring events, and this can be displayed as a day or month view. Under "medications" tab, a list of the medications can be entered along with the time, strength, dosage, frequency and indication. Users are reminded to take their medications from the tablet device, and enter their compliance to generate a compliance report. Under "health" tab, vital signs or point of care information such as weight, blood pressure or blood glucose levels can be entered through the tablet, or electronically linked from the a monitoring system (weighing scale, glucometer or blood pressure cuff) to the web portal. A questionnaire can also be generated and questions can be tailored to cancer patients i.e. pain level measured using a Likert-scale. Under "contacts" tab, user can enter caregivers or healthcare teams' contact information, and they can be contacted directly from the tablet. Finally the "report" tab generates reports on all the aforementioned functions. Of note, automatic reminders can be generated and sent to providers if tasks are not completed or certain threshold of vital signs are met. For the purpose of this study, we are asking patients to enter their exercise data. They are encouraged to use other functions to assist with care coordination but are not required to do so.

Figure 4: Main profile page on the PointClick Care web portal



6.3. GO-EXCAP Mobile App

We plan to integrate the content of the EXCAP exercise program into the PointClick Care mobile app (Figure 5). Older patients will participate in the EXCAP exercise program and enter exercise data into the mobile app. In addition, they will complete a symptom inventory and enter any barriers to exercise into the mobile app weekly. The study team (physiologist) logs into the web portal 2x/week to monitor intervention adherence, provide feedback, and adjust exercise prescriptions. These recommendations are available to the patients - they are automatically displayed via the mobile app daily. Patients can interact with the physiologist directly or via the mobile app.

Symptom reporting and management is an important component of our intervention because symptoms are common barriers to exercise. Based on our pilot data,[16,90] we selected 15 common symptoms experienced by patients with MN based on the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).[91] We will assess symptoms weekly. These symptoms will be recorded on the web portal (described above). Study coordinator will log on to the web portal at least weekly to ensure that the symptom surveys are being completed. If the symptom surveys are not completed, the study coordinator will remind the patient during the weekly calls. For each symptom, we will use standardized severity-based algorithms and self-management strategies based on established protocols (Figure 6).[92–94] A symptom report will be generated at clinic visits. In addition, these reports will be provided to the clinic nurses on a weekly basis.

Therefore, the mobile app serves as a tracking, teaching, and self-management device that is tailored to the individual. We will adapt the intervention content, format, and delivery of the app based on feedback from patients.

In the case that participants are unable to use the PointClickCare mobile app (i.e. company no longer operating), we will administer the exercise surveys and symptom inventories as REDCap surveys. The surveys will be disseminated via email. If the PointClickCare mobile app is no longer available, current subjects who are enrolled in the study will transition to use of the REDCap surveys and will terminate use of the mobile app. The previously collected data and subsequent analysis will remain unaffected and there will be no changes made to the study aims. Current subjects will be verbally notified of this change.

Figure 5: Proposed GO-EXCAP Mobile App

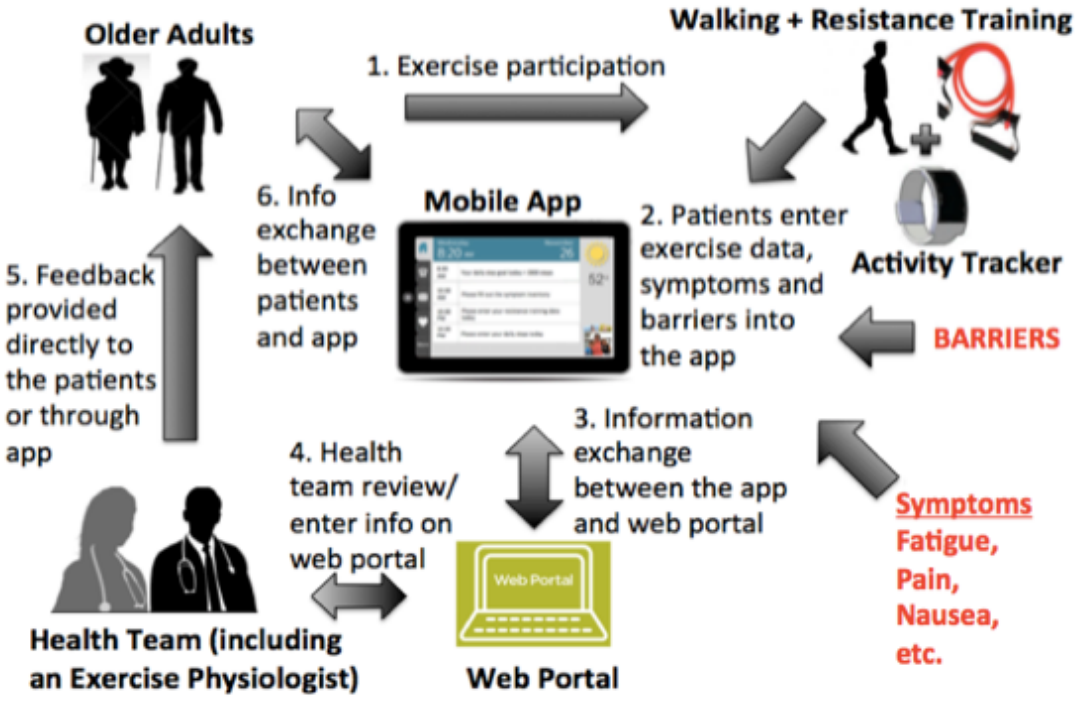


Figure 6: Example of severity-based algorithm/self-management strategies

In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?

None	Mild	Moderate	Severe	Very Severe
No advice	- Did the fatigue stop you from exercising? - Have you had recent blood work? - Assess pain, distress, sleep hygiene, and nutrition - Review energy conservation, sleep hygiene, physical activity, nutrition, etc.		- Did the fatigue stop you from exercising? - Same as mild/moderate - If you have not already contacted your medical team, we recommend you to contact them	

7.0. Treatment Protocol

7.1 Study Outline

Patients who receive HMA and other outpatient chemotherapy typically have declines in their blood counts during the 1st month of therapy before improvements are noted. Therefore, we will initiate our intervention at cycle 2 the earliest. HMA and other common chemotherapy are administered daily as an infusion or subcutaneous injection for 5-10 days every 4 weeks. There are outpatient chemotherapy that are pill-based as well (e.g., enasidenib, ivosidenib) and are also dosed every 4 weeks. We will consent patients and they will complete measures during routine visits. They will complete baseline measures during the 4th week of a chemotherapy cycle up to day 1 of the subsequent cycle prior to chemotherapy administration (study week 0) (Figure 1). The intervention will start during the 1st week of of a new cycle (study week 1) and will last 8± 4 weeks. The post-intervention measures will be completed 2 cycles later during the 4th week of the cycle (study week 8± 4). To illustrate this, if the intervention starts in cycle 2 week 1, baseline measures will take place on cycle 1 week 4, and post-intervention assessment will place on cycle 3 week 4. If the intervention starts in cycle 6 week 1, baseline measures will take place on cycle 5 week 4, and post-intervention assessment will place on cycle 7 week 4.

At the screening visit, we will confirm if the patient is eligible using the eligibility criteria above. Once we confirm their eligibility, we will obtain either in-person or verbal consent. The patient will then complete a demographic questionnaire that asks about the participant's age, gender, race, ethnicity, education level, marital status, employment status, and Eastern Cooperative Oncology Group (ECOG) performance status as well as their cancer and treatment characteristics (see Section 7.2).

For Aim 1, one interview will be conducted with each participant in a private space for approximately 30 minutes. First, we will explain the rationale and demonstrate the use of the GO-EXCAP Mobile App. Second, we will elicit preferences for the content, format, and delivery of the intervention (Table 2). Collectively, the findings will be used to adapt the intervention.

Table 2: Intervention features and example of adaptation based on feedback from patients

Feature	Goal	Example of Adaptation
Content	To confirm the frequency, intensity, and duration of the exercises and appropriate percentage increment of steps and resistance band training exercise.	If patients report that they are less able to exercise on the days of chemotherapy, we will plan to maintain rather than increase the number of steps and intensity of resistance training exercises during those days.
Format	To elicit preferences regarding the format of the training manual	If patients prefer an electronic training manual, we will develop this and incorporate it into the mobile app.

	(i.e. paper, audio, video, or a combination).	
Delivery	To elicit preferences in the administration of the intervention (i.e. in-person, through the app, or a combination of both).	If patients prefer the intervention to be administered entirely through the app (without the baseline visit with an exercise physiologist), we will develop a video to demonstrate the exercise techniques on the mobile app.

For Aim 2: Participants will be provided with an activity tracker to measure daily steps over 4-7 days. After baseline measures (including blood samples), participants will meet with an exercise physiologist in-person and/or via zoom/phone who will demonstrate how to perform the exercises and the basic features of the mobile app. Both the assessments and teaching will be conducted either at Dr. Mustian's Physical Exercise, Activity and Kinesiology (PEAK) laboratory and/or virtually via zoom/phone. Alternatively, if requested, certain assessments and teaching will be completed at the cancer center. Patients will be provided with the GO-EXCAP Mobile App on a tablet which will be equipped with cellular connectivity. The Exercise Physiologist and/or study coordinator will ensure successful set up of tablet device for the subjects and he/she will also provide in-person instructions on the use of the mobile app. The study coordinator will also be available to answer any potential subsequent questions in regards to the use of the app.

For Wilmot affiliated sites (except for Olean, Dansville, and Wellsville where research activities will not be conducted), similar procedures will be used if participants are willing to travel to Wilmot Cancer Institute/Strong Memorial Hospital. For participants who are not willing to travel, our study coordinator will perform assessments at the affiliated sites. Blood samples will also be collected. Teaching will be conducted either in-person or via zoom. Assessments that are required to be performed at the PEAK lab will be omitted if participants are not willing to travel..

From study week 1-8 (± 4), participants will perform the exercises at home. Participants will enter their daily steps from the activity tracker, time spent for resistance band exercises, and exercise intensity into the mobile app. They will enter any barriers to exercise on the app and complete the PRO-CTCAE questionnaire weekly. These data will be transferred automatically from the app to a Web portal. The study team (physiologist) will log into the Web portal twice a week to monitor adherence, provide feedback, and adjust exercise prescriptions. These recommendations will be available to each participant via the app or directly. Participants can interact with the physiologist via the app or directly. The study coordinator will also call the patients weekly to answer any questions. The algorithms for symptom reporting and management developed in Aim 1 will be incorporated into the app. To ensure safety, participants will answer questions weekly on the app to determine ongoing appropriateness of exercise (e.g., no interval cardiac symptoms) and ensure there are no new medical contraindications to exercise.[95]

Mid-intervention (study week 3-5): We will conduct an in-person or zoom/phone interview (approximately 30 min) with participants. A three-week window will be used to conduct interviews with participants. App functionality, usability, and barriers to adherence will be elicited.

Post intervention (study week 8± 4 weeks; chemotherapy delay is common due to cytopenias): We will collect the same measures as baseline (including blood samples) and usability data. An exit interview (approximately 30-45 min) will be conducted with participants either in-person or via zoom/phone to elicit app functionality, usability, and barriers to adherence. Participants who complete both the baseline and post-intervention measures will receive $50. They may keep the exercise kit and activity tracker (value $150).

Procedures at the affiliated sites will follow the baseline assessments.

7.2. Baseline Assessment of the Participants

Demographics, clinical and treatment/cancer characteristics will be collected.

7.2.1. Socio-Demographics and Clinical Characteristics

Patient's age, race, ethnicity, gender, highest level of education achieved, employment status, marital status, and ECOG performance status will be captured from the patients. The socio-demographics and clinical characteristics will only be collected at baseline.

7.2.2. Cancer and Treatment Characteristics

Type of myeloid neoplasms, prior hematologic malignancies, cytogenetic risk group and treatment regimen will be abstracted from the medical records. This information will be collected at baseline only.

7.2.3. Outcomes of Interest (Baseline and post-intervention unless otherwise specified)

For patient-reported questionnaires, if we are unable to provide assessment forms to the participants, these will be mailed to them at least 1 week ahead of time. For assessments that needed to be conducted in-person (including blood sample collection), these may be omitted when appropriate for safety of the patients.

7.2.3.1. Physical Function

Short Physical Performance Battery (SPPB): The SPPB is an objective physical assessment evaluating lower extremity physical function.[96] It is comprised of a four-meter walk, repeated chair stands and a balance test. Impairment on SPPB testing has been shown to be predictive of short-term

mortality and nursing home admission in community-dwelling older adults. We will also perform the virtual SPPB via the phone/zoom, which evaluates the participants' perceived ability to perform above tests (walking, repeated chair stands, and balance).

7.2.3.2. Fatigue

Brief Fatigue Inventory (BFI): BFI is a 9-item, patient-report instrument with established reliability and validity that we have used in previous studies.[97] The BFI allows for the rapid assessment of fatigue level in cancer patients and identifies those patients with severe fatigue. The reliability and validity of the BFI were demonstrated in a study of 305 cancer patients and 290 community-dwelling adults.[98]

7.2.3.3. Depression

Center for Epidemiological Studies Depression Scale (CES-D): The CES-D is a 20-item depression scale developed and validated for use with a variety of populations.[99] It is in a format similar to that of the Beck Depression Inventory, but with less emphasis on physical symptoms of depression that may be confounded with disease symptoms or treatment side effects. It has been shown to reliably and validly measure depression in cancer populations.[100]

7.2.3.4. Quality of Life (QOL)

*Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu)***:** *T*he FACT-Leu scale was created by combining the Functional Assessment of Cancer Therapy-General module (FACT-G) and a sub-scale made up of 17 leukemia-specific items.[101] It been tested and determined to be a valid, reliable, and efficient instrument for evaluating leukemia-specific health-related QoL.

7.2.3.5. Self-efficacy for Exercise and Exercise Adherence

Self-Efficacy for Exercise scale: This is a 9-item scale to measure self-efficacy for exercise and higher score indicates higher self-efficacy.[102]

Actigraphy (research-grade). The actigraph is a small, lightweight, non-invasive device worn on the waist (clipped to clothes or worn as a waistband). The actigraph contains an accelerometer that quantifies duration and intensity of physical activity and sedentary behavior throughout the day and week. We will use an actigraph that provides calculated energy expenditure values for active energy expenditure in kilocalories and total energy expenditure in metabolic equivalents per time in kilocalories/min/kg. We will use software supplied by the manufacturer

to determine bouts of moderate or higher activity during each assessment period (T1, T2, and T3). This is a research-grade device that complements the commercial-grade wrist-worn Garmin activity tracker.

Exercise Readiness: This will be assessed using the Physical Activity Readiness Questionnaire (PAR-Q+) form. This is designed to assess patients' readiness to participate in more physical activity or engage in a fitness appraisal.

7.2.3.6. Other Geriatric Assessment Measures

Activities of daily living (ADL): ADLs are measures of self-care. ADL independence will be assessed using the Katz Index of Independence in Activities of Daily Living, commonly referred to as the Katz ADL. The Katz ADL is the most appropriate instrument to assess functional status as a measurement of the client's ability to perform activities of daily living independently. Clinicians typically use the tool to detect problems in performing activities of daily living and to plan care accordingly. The Index ranks adequacy of performance in the six functions of *bathing, dressing, toileting, transferring, continence, and feeding.* Clients are scored yes/no for independence in each of the six functions. A score of 6 indicates full function, 4 indicates moderate impairment, and 2 or less indicates severe functional impairment.

Instrumental Activities of Daily Living (IADL): Self-reported functional status will be assessed using the IADL subscale of the Multidimensional Functional Assessment Questionnaire: Older American Resources and Services (OARS). The IADL subscale consists of seven questions rated on a three-point Likert scale. It measures the degree to which an activity can be performed independently.

Fall History: A self-reported history of falls in the past three months will be recorded. A history of a recent fall has been demonstrated to be independently predictive of increased risk for chemotherapy toxicity in older cancer patients.[20]

6-minute walk test (6MWT): The 6MWT measures functional endurance and aerobic capacity.[103] It measures the distance walked by the patient over a time of 6 minutes. We will also assess gait analyses using the BTS G-SENSOR. The BTS G-SENSOR is a small non-invasive device worn on a waist belt to provide functional evaluation of walking that includes accelerometers, gyroscopes, and magnetometers, allowing the spatio-temporal parameters of subject's gait to be measured as well as their pelvic rotations and swing leg accelerations. It provides objective and quantitative data that is related to muscles activity and kinematic parameters.

Nutrition: Screening for nutritional deficit will be performed with body mass index (BMI) evaluation and self-reported weight loss.

Cognition; Montreal Cognitive Assessment (MOCA): A 30-point cognitive screen test with excellent sensitivity for individuals with mild dementia and mild cognitive impairment. It can also be used to trend changes in cognitive status over time. If in-person assessment is not possible, MOCA-blind will be conducted via zoom/phone.

Comorbidity (baseline only); *OARS Physical Health Section:* Patients self-report their coexisting medical conditions and also rate the degree to which their illness causes impairment in daily activities. The OARS Physical Health Section has been shown to correlate significantly with health professional ratings of comorbidity as well.

Social Support (baseline only); OARS Medical Social Support survey: A 13-question survey asking patients to identify the number of support persons involved in their medical care as well as the degree to which they felt supported in a variety of situations.

Medications (baseline only): We will record all prescription and non-prescription medications, dosage and frequencies from the medical records. Polypharmacy is defined as the use of 5 or more medications.

7.2.4. Complete blood count (CBC)

Blood counts measured by standard CBC with differential procedures will be abstracted from the patient's medical record.

7.2.5. Muscle mass testing

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 have the option to be 4 hours fasted, although it is not required. Participants need to be abstained from alcohol and diuretics (unless prescribed) for 48 hours, well hydrated (water only), and voided completely prior to assessment. 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 (proximal phalanx of the 3rd finger and the radiocarpal joint), 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.

7.2.6. Muscle strength testing

Upper extremity muscle strength will be assessed using a handgrip dynamometer.[104]

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 in anatomical position; the elbow joint angle will be held constant at 90 degrees with the medial distal humeral epicondyle 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. The surgically involved arm(s) will be noted for data analysis. The handgrip dynamometer test has been previously used in a number of URCC NCORP protocols and has shown to be a reliable clinical method of assessing upper extremity strength.

Lower and upper extremity muscle strength will be assessed using the isokinetic muscular strength test. We will use an isokinetic knee flexion/extension for lower extremities and seated shoulder diagonal for upper extremities. If seated shoulder diagonal cannot be performed (e.g., prior shoulder injury), elbow flexion/extension will be performed instead. An 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 exercise physiologist will be present during the test to ensure proper form and subject comfort. After the warm up set, subjects will complete a single set per side. Subjects will exert maximal force through their entire range of motion, moving at a set speed in degrees per second against the lever arm. Subjects will rest for approximately 3 minutes between sets. This isokinetic protocol will allow us to measure peak torque, maximal work, total work, and average power for each movement. We will use a Biodex System 4 Pro, which has been used successfully in over 1,000 research studies and is both safe and accurate in measuring muscular function.[120]

Muscle activation during strength testing (isokinetic muscular strength test) will be assessed using electromyography sensors. The BTS FREEEMG 1000 is a wireless EMG system that directly measures muscle activity. The system uses eight miniaturized probes with active electrodes for signal acquisition and transmission for EMG, angles, speed, acceleration, and pressure assessment. The probes include on-board memory. The subject will have full range of motion during task execution. BTS FREEEMG can measure the movement of any muscle activity, is analyzed by the BTS EMG-Analyzer software, and integrates with the BioDex. Probes will be applied to subject's skin surface over the muscle used during knee flexion and extension and elbow flexion extension repetitions.

Height and weight will be assessed using the Blue Bell Bio-Medical SR Instruments Model 500. We will also measure waist circumference with a Gulick tape measure. Height, weight, and waist circumference will be assessed at each PEAK lab visit to help estimate body composition. Waist circumference will be measured from the narrowest portion above the umbilicus and below the zyphoid process.

7.2.7. Heart Rate Variability (HRV): HRV measures variation in consecutive heartbeat intervals. It provides acute measures of physiological recovery. HRV data will be collected for 5 minutes and assessed using the Firstbeat® system. Firstbeat® is a portable device consisting of two electrodes (one above and below the ribcage) placed on the patient.

7.3. Post-Intervention Assessment of the Participants

At the post-intervention assessment, all subjects will continue to wear their Garmin activity tracker for 4-7 days. Study staff will collect the tablet from the participants. Participants will keep the EXCAP exercise kit. In addition to the assessments above, we will assess the intervention usability. We will also conduct an exit interview either in-person or via zoom/phone to elicit app functionality and barriers to adherence to the intervention.

7.3.1. Intervention Usability[105,106]

System Usability Scale is a standardized questionnaire used to assess participants' perceptions of usability. This robust and reliable scale consists of a 10-item questionnaire with each item rated on a 5-point Likert scale (see Appendix). The scores for each question will be converted to a new number (odd-numbered questions are calculated as the scale position minus 2, and even-numbered questions are calculated as 5 minus the scale position), added together, and then multiplied by 2.5 to get the final score (ranging from 0 to 100).

7.4. Assessment of inflammatory markers (Exploratory Aim 2)

Using blood samples, we will assess the blood concentrations of several inflammatory markers. All blood draws will occur in the Wilmot Cancer Center, a UR-affiliated lab, or medical office if needed (in the latter case, we will use a trained study staff member to transport the samples to our storage facility). The location will be selected to minimize subject burden and if possible we will perform blood draws at the same time as a regularly scheduled medical blood draws. The blood will be drawn by trained staff. The time of day will be noted, with future assessments at approximately the same time of day during post-testing. Fasted blood samples (4-6 hours prior to blood with encouragement to maintain hydration) will be drawn. If the blood sample is not fasted, we will still

collect the blood sample and note the last time the person ate in the research record. All subjects will be provided with a $10 gift card for a café at URMC.

A total of approximately 50 mL of blood (around 4-5 tablespoons) will be drawn at baseline and post-intervention. All tubes will be collected by a study team member, processed, and then transferred to a secured -80°C freezer in lab space maintained by Dr. Janelsins in the Department of Surgery. We will collect the following:

1. One red-top tube for serum (9 mL each). This tube will be inverted 10 times, allowed to clot for 30 minutes at room temperature, centrifuged for 15 min at 1600 *g* and then frozen at -20°C or -80°C. These will be used to assess inflammation (cytokines, etc.).
2. Two purple-top EDTA tubes for DNA methylation and plasma analyses (9 mL each, 18 mL total). This tube will be inverted 10 times and allowed to sit at room temp for 30 minutes, centrifuged for 15 min, and then frozen at -20°C or -80°C.
3. Two green-top tubes for peripheral blood mononuclear cells (9 mL each, 18 mL total). These will be pre-cooled and processed per SOP. This tube will be inverted 10 times and allowed to sit at room temp for 30 minutes, centrifuged for 15 min, and then frozen at -20°C or -80°C.
4. Two paxgene tubes for gene expression analyses (2.5 mL each, 5 mL total). This tube will be inverted 10 times and allowed to sit at room temp for 2-24 hours. Then they will be frozen at -20°C and moved to -80°C for long-term storage.

Inflammatory cytokines will be assessed using the latest available technology (e.g., *in vitro* enzyme-linked immunosorbent assay; ELISA). These assays will assess the concentration of inflammatory cytokines including TNFα, sTNFR1, sTNFR2, IL-1β, IL-6, sIL-6R, IL-8, IL-10. Cytokine analyses will be performed at Dr. Michelle Janelsin's lab.

For DNA methylation analysis, genomic DNA will be isolated from peripheral mononuclear cells with a DNeasy Blood and Tissue Kit (Qiagen) and quantified with the NanoDrop 1000 spectrophotometer. *TNFα* gene promoter methylation will be quantified using bisulfite pyrosequencing.[107] Briefly, genomic DNA (1000 ng) will be bisulfite converted (converts cytosine to uracil but leaves 5-methylcytosine residues unaffected) using the Epitect Plus Bisulfite Conversion Kit (Qiagen). Using *TNFα*-specific primers, the region of interest will be amplified by PCR with the PyroMark PCR kit (Qiagen). Pyrosequencing analysis will be used to measure DNA methylation in the *TNFα* promoter region from −360 to +50 base pairs (containing 12 CpG sites) using the PyroMark Advanced Q24 (Qiagen).[108] We selected these 12 CpG sites based on a prior study which showed that total methylation and methylation at -245 bp correlated with serum TNFα levels.[108] Methylation at -170bp and -120bp also predicted response to a lifestyle behavioral intervention.[108] In addition, the majority of known regulatory transcription factor binding sites (e.g. NF-κB, Sp-1, Egr1)[109] within the *TNFα* gene promoter region are located in this region. Other cytokine gene promoter methylation will be analyzed as per *TNFα* (promoter regions will be determined based on previous studies).[110–112] DNA methylation analyses will be performed at Dr. Martha Susiarjo's lab.

For gene expression, RNA will be extracted using the RNeasy Mini Kit (Qiagen) according to the manufacter's protocol and quantified using the NanoDrop spectrophotometer.[107] cDNA will be will be prepared by RT-PCR using Superscript IV reverse transcriptase and random hexamers (Invitrogen). qPCR analysis will be conducted using the Applied Biosystems QuantStudio 5 Real-Time PCR system using *TNFα* and cytokine gene-specific primers. Relative expression of *TNFα* and related genes will be calculated using the comparative Ct method, and measurements will be normalized to expression of two reference genes. Gene expression analyses will be performed at Dr. Martha Susiarjo's lab.

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 samples will be de-identified before being stored.

7.5. Data specimen banking for future research

We will bank blood samples for use in future studies to assess other inflammatory markers and genome wide DNA methylation analysis. We will also keep remaining samples for future research by Dr. Loh and her research team. The consent form includes a section asking whether subjects agree to have their samples banked for future studies by Dr. Loh and her research team.

Genome wide DNA methylation [with subsequent DNA methylation age (DNAm age analysis) will be performed at Genomic Shared Resource at Roswell Park Cancer Institute. We are in the process of obtaining an MTA with Roswell. After processing, stored blood is aliquoted and identified using study ID. No patient identifiers are included in the label. Aliquotes will be sent to Roswell Park. DNA methylation microarray assay will be performed using the Illumina Infinium® Methylation EPIC Array platform, an oligonucleotide array that interrogates >850,000 CpG dinucleotides per sample, in accordance with the manufacturer's instructions. The raw data will be processed by the R package "minfi", and converted to methylation ß-value, ranging from 0 to 1, with 0 being unmethylated and 1 being fully methylated, to represent the methylation level of each CpG site. Potential residue batch effects will be inferred from the data using a Surrogate Variable Analysis (SVA), and the ComBat algorithm will be used for correction. Rigorous quality-control criteria will be used for filtering at both the locus and sample levels. The final data will be supplied to the DNAm age estimation algorithms.

8.0. DATA HANDLING AND STATISTICAL CONSIDERATIONS:

8.1. Data Handling

8.1.1. The same protocols and procedures for data quality and control that are readily used for the NCI Community Oncology Research Program (NCORP) Research Base protocols currently being overseen by our office (which have accrued over 1,000 patients in the previous year) will be used for this study. Patients will fill out forms generated from RedCap and this information will be entered into RedCap (Section 9.5). Study personnel will perform SPPB and the scores will be entered into RedCap.

8.1.2. It is anticipated that allowing for the appropriate number of evaluable participants and by checking self-report measures for completeness, we will have a full complement of data. Every effort will be made to encourage and facilitate participants' completion of all questionnaires and all items on the questionnaires for each study assessment. In the event that missing data occur, every effort will be made to contact participants via phone and obtain the data or to find out why the questionnaires or items are missing. The reasons for missing data will be documented. Missing questionnaire items will be treated in accordance with the documented scoring procedures. Although it is very unlikely that missing values will not occur randomly, we will confirm their randomness. Multiple imputation[113] will be applied to (1) give more accurate statistical tests and standard errors for key treatment effect parameters and to (2) give some indication of the sensitivity of the analyses to missing data. The causes and pattern of the missing data will be examined and taken into consideration in the design of future studies.

8.1.3. Data collected with the tablets and Garmin activity trackers will only be accessed by the following: 1) The research team including the exercise physiologist, 2) The treating physician and their designee, and 3) PointClick Care company. The research team and exercise physiologist will each have a username and password to access the tablets and devices. The PointClick Care company will have access to the data on the tablets. As discussed above, PointClick Care encrypts all PointClick Care data transferred between backend servers and the tablets. Communications to the server is validated by signed trusted server certificate. Data at rest is always encrypted. PointClick Care caches data on the tablet, and stores data on a PointClick Care server. On the tablet the cache in encrypted, the backend server hosts a Microsoft SQL Server database. The volume used by SQL Server is encrypted. Only the PointClick Care app, with a valid authentication key, can read this data. If the electronic data is breached, PointClick Care has a means to disable the PointClick Care app on a tablet. This feature only works, however, if the Tablet is connected to the server. We will also inform the study participants if the breach has occurred. Users are not able to exit the app from the tablet. If the tablet is lost or stolen, PointClick Care has a means to disable the PointClick Care app as soon as it is turned on. If the tablet is

broken, it will be replaced with a new one (all data within the tablet will be erased).

8.1.4. We are currently communicating with OPRA regarding the need for a data use agreement with the PointClickCare company.

8.2. Data Analysis and Sample Size:

8.2.1. Analysis Plan for Aim 1

Our planned sample size (N=15) will allow us to achieve thematic saturation. We will conduct and audio-record all interviews, which will be transcribed by a professional transcription service. We will analyze the qualitative data using grounded theory and constant comparative methods, with coding to structure data into categories and create groups according to the broader issues or themes.[114] An audit trail of the coding activity will be kept. We will critically examine the data collection and analysis process and reach consensus on key themes from patient feedback to be used to adapt the intervention in preparation for Aim 2.

8.2.2. Analysis Plan for Aim 2

The feasibility of the GO-EXCAP Mobile App will be evaluated based on the following: a) Percentage of patients wearing the activity tracker and entering resistance exercise data into the mobile app and b) Percentage of patients performing both walking and resistance exercises during the study period days. Recruitment rates (percentage of patients who are approached and agree to enroll) and retention rates (percentage of patients who are enrolled and complete post-intervention assessments) will also be described

We will consider the intervention feasible if 1) ≥70% of patients wear the activity tracker and enter resistance exercise data into the mobile app on at least 50% of the study period days, and 2) ≥70% of patients performed both walking and resistance exercises on at least 50% of the study period days. We chose these criteria based on our previous mobile app study[16] and on published exercise studies in older patients with AML.[29,30] We will report percentage of adherence with 95% exact confidence interval (CI) calculated by the Clopper-Pearson method. We anticipate that about 20-30% of the participants will withdraw before post-intervention assessment due to rapid disease progression or death. These patients will not be included in the feasibility analysis because their withdrawals from the study are not related to the intervention. With 25 patients enrolled we anticipate at least 17 patients to be evaluable for our feasibility aims. When we estimate the percentage of adherence, a 95% CI will span approximately +/- 25%. For example, if we observe 12/17 (71%) patients complete the tasks, the CI will be 44-90%.

We will also tabulate the recruitment rates, retention rates, and intervention usability, and collect the reasons patient decline to be enrolled. In addition, we will evaluate the distribution and describe the following measures using descriptive statistics: 1) activity levels, 2) physical function (SPPB/vSPPB), 3) fatigue (BFI), 4) depression (CES-D Scale), 5) quality of life (FACT-Leu), and 6) Other geriatric assessment measures. Differences in activity levels, physical function, fatigue, depression, quality of life, and other geriatric assessment measures between pre- and post-treatment will be assessed using paired t-tests or Wilcoxon signed rank tests. Anticipated sample size of more than 12 patients with baseline and follow-up data will be sufficient to obtain the preliminary estimates of the outcomes measures.[115,116]

Qualitative data from the exit interviews will be analyzed as per Aim 1. Interviews will be conducted, audio-recorded, and transcribed. Two trained "coders" will utilize a multi-step process using coding and content analysis, with coding to structure data into categories and creating groups according to the themes.[114] We will identify themes that emerge within each content area. I will discuss these results with my study personnel and Dr. Mohile every two weeks to critically examine the data collection and analysis process, provide critical feedback on emerging codes, and reach consensus on principal themes to be used to optimize the intervention. For every five patients, we will use the principal themes to optimize the intervention in an iterative process. We will identify patients who are not entering their daily steps or the resistance training data into the app. For these patients, we will elicit specific barriers and explore the relationship between these barriers and exercise adherence. We anticipate that the barriers to exercise adherence will be modifiable (e.g., symptoms, lack of self-motivation, and lack of knowledge of the benefits of exercise) or non-modifiable (e.g., caregiving obligations, hospitalizations). The intervention will be optimized based on the following modifiable barriers, such as: a) Symptoms (e.g., fatigue, soreness): Monitor symptoms with automated self-management feedback and/or notification to the healthcare team; b) Lack of self-efficacy: Provide reassurance and motivational messages through the app; c) Lack of knowledge: Provide education on the benefits of exercise.

8.2.3. Analysis Plan for Exploratory Aim

Descriptive analysis will be used to describe cytokine gene promoter methylation (global % methylation of the gene promoter region and % methylation of each of the identified CpG sites) and gene and protein expression at baseline and post-intervention. Changes from baseline to post-intervention will be compared using paired t-tests. We will use Spearman's correlation to assess relationships between methylation status and gene and protein expression, as well as activity level and clinical measures. We will adjust for multiple comparisons using the Benjamini–Hochberg method.[117]

9.0. DATA MANAGEMENT

9.1. Data Collection Table (Aim 2)

	SCHEDULE OF DATA COLLECTION			
	Eligibility and Consent Form	**Baseline Assessment (week 0)**	**Mid-Intervention Assessment (week 3-5)**	**Post-intervention Assessment* (week 8± 4)**
Written Informed Consent	X			
Demographics		X		
Cancer and Treatment Characteristics		X		
Qualitative Interview			X	X
Activity Levels (Activity Tracker)		X		X
Exercise Habits and Readiness		X		
Short Physical Performance Battery[b]/Virtual Short Physical Performance Battery		X		X
Brief Fatigue Inventory (BFI)		X		X
Center for Epidemiologic Studies Depression Scale (CES-D)		X		X
Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu)		X		X
Self-Efficacy for Exercise		X		X
Actigraphy[b,d]		X		X
Geriatric Assessment Measures • Activities of Daily Living		X		X

• Instrumental Activities of Daily Living • Fall History • 6-Minute Walk Test[b,d] • Montreal Cognitive Assessment (MoCA or MOCA Blind)				
Bioelectrical Impedance System[a.b,d]		X		X
Handgrip Dynamometer[b,d]		X		X
Muscle Strength Testing[a.b,d]		X		X
Heart Rate Variability[a,b,d]		X		X
Feasibility metrics				X
System Usability Scale				X
Complete blood count (from electronic medical record)		X		X
Blood samples[b]		X		X

[a]If patient elects to undergo the assessments at the cancer center instead of the Physical Exercise, Activity and Kinesiology laboratory, these assessments will not be conducted.
[b]May be omitted for patient safety (i.e., if in-person assessments are not possible)
[d]If research activities are conducted at Wilmot affiliated sites, these assessments may be omitted

9.2. All hardcopy research records will be stored onsite in the URMC, in locked research files at the James P. Wilmot Cancer Center. The Cancer Center is secured with electronic key cards. Offices within the Cancer Center are again secured by key and data is kept in locked file cabinets. Electronic research records are stored on the URMC's password secured and firewall protected networks. These are the same methods of security used for patient medical records. All study data (including the electronic data kept by the PointClick Care company) will be kept for a period of 7 years after the study and all reports and publications are complete.

9.3. All data collected for the current study will be used in post hoc analyses as appropriate. Data will not be used for future studies without prior consent of the patient. The patient's individual research record 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 URMC after completion of the study. Study results will be presented at professional meetings and published.

9.4. The study coordinator will assign a numerical study ID to each participant once they have signed the consent form (chronologically based on the data they signed consent i.e., 001, 002, 003…). All study forms and questionnaires will use this number and the participant's first, middle, 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. This linkage information will only be accessible to the study coordinator, study investigators, and the individuals responsible for maintaining the database.

9.5. Additionally, data on the socio-demographics, clinical, cancer and treatment characteristics will be collected and managed by the research teams at URMC using REDCap electronic data capture tools hosted at URMC.[118] We will also evaluate the medical records for clinical characteristics and outcomes, and utilize REDCap to collect and manage this information.

9.5a. URMC provides the following information on the **REDCap program:** **"**Vanderbilt University, in collaboration with a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data, called REDCap (Research Electronic Data Capture). The REDCap system is a secure, web-based application that is flexible enough to be used for a variety of types of research. It provides an intuitive interface for users to enter data and real time validation rules (with automated data type and range checks) at the time of data entry. REDCap offers easy data manipulation with audit trails and functionality for reporting, monitoring and querying patient records, as well as an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). Through the REDCap Consortium, Vanderbilt has disseminated REDCap for use around the world. Currently, over 240 academic and non-profit consortium partners on six continents with over 26,000 research end-users use REDCap.[119]

9.5b. According to the Clinical and Translational Science Institute (CTSI), REDCap is supported with the following means. "The *CTSI Informatics Core*, a unit of the SMD *Academic Information Technology (AIT) Group,* will serve as a central facilitator for data processing and management. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team, with planning assistance from the *AIT-CTSI Informatics Core*. The iterative development and testing process results in a well-planned data collection strategy for individual studies."[119]

9.5c. The CTSI states that regarding security, **"**REDCap servers are housed in a local data center at the University of Rochester and all web-based information transmission is encrypted. REDCap was developed in a manner consistent with HIPAA security requirements and is recommended to University of Rochester researchers by the URMC Research Privacy Officer and Office for Human Subject Protection.[119]

10.0. RISKS/BENEFITS

10.1. Risks

There are two potential risks associated with participation in the proposed study: 1) physical harm associated with intervention procedures, and 2) loss of confidentiality.

10.1.1. 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. A transient increase in blood pressure may occur with all types of exercise. Although unlikely, a low to 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 proposed low to moderate intensity exercise program is minimal.

10.1.2. In terms of loss of confidentiality, quantitative data 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.

10.2. Benefits

Patients participating in the first aim will be paid $30 and those participating in the second aim will be paid $50 for their participation in the form of gift cards. For Aim 1, patients will receive the gift cards immediately following the interviews. For Aim 2, patients will be paid for completion of the post-intervention assessment. Patients in Aim 2, patients may also keep the exercise kit and activity tracker at study completion (value $150).

11.0. DATA SAFETY AND MONITORING

Only adverse events (AEs) related to the study intervention or procedures will be reported. In other words, AEs related to cancer treatment will not be reported.

11.1. Adverse Event Reporting Requirements

11.1.1. Adverse events will be reported using the URCC Adverse Event form and/or as required by the Cancer Center Clinical Trials Office.

	Grade 1	Grade 2			Grade 3				Grade 4		Grade 5	
		Unexpected		Expected	Unexpected		Expected		Unexpected	Expected	Unexpected	Expected
	Unexpected and Expected	with hospitalization	without hospital-ization		with hospitalization	without hospitalization	with hospitalization	without hospitalization				
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	Not Required	10 Calendar Days	10 Calendar Days	Not Required	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days
Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.												

11.1.2. Adverse events will be reported in accordance with the following guidelines:

11.1.3. Adverse event reports will be submitted in one of the following ways:

(1) By email: (pdf)

(2) By mail:

(3) By fax:

11.1.4. An unexpected adverse event is defined as any adverse experience, the specificity or severity of which is not consistent with the risk information. This is a minimal risk study as both exercise and mobile app-driven interventions have been shown to improve outcomes in community-dwelling older adults.

11.1.5. A serious event refers to any event in which the outcome results in any of the following: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability, incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the participant and may

require medical or surgical intervention to prevent one of the outcomes listed in this definition. We anticipate that any serious events will be related to standard of care cancer treatments and not due to the intervention. We will not collect adverse events related to cancer treatments.

11.1.6. Adverse events will be reported in accordance with institutional policies (University of Rochester, Research Subject Review Board, local IRB, URCC CCOP, CTO, and DSMB) as per their requirements.

11.2. Data Safety Monitoring

11.2.1. All adverse events requiring reporting will be submitted to the current Project Coordinator as described in Section 11.1. Serious adverse event reports will be forwarded to the study chair and the Data Safety and Monitoring Committee (DSMC). Adverse events are entered into a protocol-specific spreadsheet.

11.2.2. Adverse event rates are monitored utilizing the spreadsheet. If a serious adverse event is reported frequently, the study chair will conduct a detailed review. The DSMC Committee Chair will be notified and will determine if further action is required.

11.2.3. The Data Safety Monitoring Committee (DSMC) will review study progress and cumulative reports of adverse events every year and as needed. An overall assessment of accrual and adverse events will enable the committee members to assess whether significant benefits or risks are occurring that would warrant study closure.

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