PROTOCOL TITLE:
Modified Application of Cardiac Rehabilitation for Older Adults (MACRO)

Principal Investigator
Daniel E. Forman, MD

VERSION NUMBER:
Version #1

VERSION DATE:
7/7/2021

NCT Number:
NCT03922529

Table of Contents

1.0 Objectives

1.1 Purpose/Objectives.

Cardiac Rehabilitation (CR) is approved for patients with acute myocardial infarction (AMI)/acute coronary syndrome (ACS), coronary artery bypass surgery (CABG), percutaneous coronary intervention (PCI), stable ischemic heart disease (IHD), heart valve repair (surgical or transcatheter), heart failure (HF), and peripheral arterial disease (PAD).[1] Yet, participation in CR is low in older adults (~13% nationally[2]), despite their being at greatest risk for harm from the dangers associated with cardiovascular disease (CVD) in old age.

Studies on CR participation among older adults cite a lack of systematic referral, delays in starting CR following hospitalization, difficulty in finding programs that are convenient and accessible, competing time demands from family, and costs of copayments as some of the reasons that CR is poorly utilized.[3] Yet, steps to automate referral, moderate costs, and simplify access have not solved underutilization. Further, home-based,[4] hybrid,[5] and tele-health[6] have been promoted as enrichments to CR, but adherence in these programs has often been low and the utility of these new formats for older adults with complex medical and geriatric challenges remains poorly explored.[7] Dr. Daniel Forman developed principles and infrastructure for a Modified Application of Cardiac Rehabilitation for Older Adults (MACRO) at the VA Pittsburgh Healthcare System (VAPHS) with the effect that participation in CR increased from <3% to ~64% (mean age 69 years). MACRO was designed to address the idiosyncratic needs of older adults, and to facilitate successful implementation of CR for this population. The goal of this trial is to more definitively study the utility of the MACRO intervention.

A key significance of MACRO is the expanded concept of risk. Aging physiology predisposes to CVD but also to disablement, multimorbidity, sarcopenia, frailty, cognitive impairment, and sensory deficiencies.[8] CVD accelerates frailty, disability, and cognitive decline.[9] Whereas risk is traditionally defined in respect to metrics oriented to the heart and CVD (and standardized as such by the American Association of Cardiovascular and Pulmonary Rehabilitation [AACVPR][10]), MACRO broadens the approach to assessment with additional functional and frailty criteria. In other words, AACVPR criteria do not provide a full assessment of risk, since functional risk are distinct, and also predict poor cardiovascular outcomes, as well as risks of frailty and disability.[7] To address this additional dimension of functional risk, the MACRO intervention impacts common geriatric challenges using comprehensive risk assessment and coordinated strategies to tailor CR to address these risks.[11]

Specific Aims/Hypotheses

Aim 1: To establish efficacy, safety and acceptability of the MACRO intervention via a RCT.
We hypothesize that after 3 months, compared to standard of care (SOC), participants randomized into the MACRO arm will have:
H1.1: Greater improvements in function as measured by Activity Measure for Post-Acute Care Computer Adaptive Test (AM-PAC-CAT) Basic Mobility Domain (primary outcome).
H1.2: Greater improvements in function as measured by accelerometry; AM-PAC CAT Daily Activity Domain; depression; frailty; self-efficacy; and quality of life. These will be collected to the extent possible in respect to local limitations that may result from fluctuations in COVID-19 prevalence.
H1.3: Greater CR participation and adherence.
H1.4: Greater impact in readmissions and hospitalization.

Aim 2: To examine the duration of benefit of MACRO compared to SOC.

H2.1: We hypothesize that relative MACRO benefits (i.e., function indices (see H1.2), adherence and readmissions/hospitalization will persist after 6 and 12 months (12 months will be captured as timing allows)

Aim 3: To explore characteristics of patients who benefit the most from the MACRO intervention.

H3.1: We anticipate functional capacity and other baseline characteristics will identify those who benefit from the MACRO intervention (exploratory).

2.0 Background

2.1 Relevant experience.

Prevalence of cardiovascular disease increases with age. Nonetheless, participation in CR decreases with age; only approximately 13% of eligible older patients enroll.[2] CR is indicated for patients with AMI/ACS, CABG/PCI, stable IHD, heart valve repair (surgical or transcatheter), PAD, and/or HF. [1]

Studies on CR participation among older adults cite a lack of systematic referral, delays in starting CR following hospitalization, difficulty in finding programs that are convenient and accessible, competing time demands from family, and costs of copayments as some of the reasons that CR is poorly utilized.[3] Yet, steps to automate referral, moderate costs, and simplify access have not solved underutilization. Further, home-based,[4] hybrid,[5] and tele-health[6] have been promoted as enrichments to CR, but adherence in these programs has often been low and the utility of these new formats for older adults with complex medical and geriatric challenges remains poorly explored.[7]

MACRO is a transformational model of care that shifts CR from a primary focus on CVD, to CR that is centered on patients themselves, i.e., individuals who usually have many age-related problems in addition to CVD. MACRO organizes care relative to patients' goals of care and composite risks. Patients are engaged, assessed for their goals and risks, and education is initiated to best facilitate informed choices regarding realistic and practical strategies. Selection of site-, home-, or hybrid-based care is based on which option will best meet that individual patient's preferences and comprehensive needs.

2.2 Significance of the research.

A. **MACRO is patient-centered CR tailored for older *complex patients with CVD.***
A central premise of MACRO is that clinical approaches to older adults with CVD must address more than their cardiovascular issues. MACRO incorporates geriatrics principles in association with CV principles as co-dominant priorities of care.

2.3 Innovation of the research.

A. MACRO responds to a critical gap in CVD management by melding CR principles with geriatric risk modifying strategies in an intentional and flexible treatment approach. MACRO is designed to optimize accessibility and effectiveness, and to augment the potential for recovery from CVD events that are highly prevalent and otherwise prognostically dire. MACRO constitutes an important advance in geriatric cardiology wherein the conventional approach to CVD care is transmuted and enriched by linking cardiovascular management to the broader complexity of aging.

B. No prior studies have tested the impact of transitions of care in CR

3.0 Inclusion and Exclusion Criteria

3.1 Screening for eligibility.

A. **Recruitment**

We will randomize approximately 374 participants over approximately 36-months, allowing for a conservative 20% dropout to allow for uncertainties in the post-COVID-19 environment.We will identify participants using 1) inpatient admission list, 2) referral from providers, 3) CR consults list, and 4) approved flyers, letters, and mailings, 5) cardiology consult lists and clinics, and 6) discharge list

B. **Randomization**

We will use the high quality pseudo-random deviate generator in SAS® (SAS Institute, Inc., Cary, North Carolina) to randomize participants to MACRO or SOC in 1:1 ratio with random block sizes chosen from small even numbers. Exact block sizes will be revealed to the rest of the study team at the conclusion of the study to prevent educated guessing. There are some key demographic differences in populations served by the study sites, as described in the Study Settings section. Thus, randomization will be stratified by site to ensure a balance between the treatment groups with respect to site by design rather than chance. To retain maximum degree of flexibility in post-COVID-19 environment, no other stratification criterion will be employed. The statistician will create schedules which link the randomization sequence number and treatment arm and will provide them to the team constructing the data management system. At randomization, a study team member will establish the link between the participant study identifier and randomization sequence number by clicking on a database function. Randomization data will only be visible to the study statistician and intervention delivery personnel. Therefore, all personnel involved in post assessments will be blind to treatment assignment.

3.2 Specific Criteria

Summary of Inclusion criteria: 1) Age ≥70 year; 2) Eligible CVD diagnosis (hospitalization or acute event for AMI/ACS, stable CAD, revascularization [CABG, PCI], valvular heart disease [specifically, surgical or percutaneous intervention for mitral regurgitation or aortic stenosis], PAD or HF [exacerbation or new diagnosis]); 3) English speaking and able to provide informed consent; 4) able to be assessed and undergo study interventions.

Summary of exclusion criteria: 1) Unstable medical condition as indicated by history, physical exam, and/or laboratory findings; 2) Presence of non-CVD conditions likely to be fatal within 12 months (e.g., metastatic cancer); 3) Severe cognitive impairment: Short Blessed with a score of 13 or greater, or cannot consent (as indicated by medical record); 4) Long-term care resident at admission with no plans to return to independent living; 5) anticipates inability to return for required reassessments.

3.3 Special Populations

Vulnerable populations (fetuses, pregnant women, children, prisoners, and institutionalized persons) and adults unable to consent will not be included in this study.

4.0 Multi-Site Research

The University of Pittsburgh will serve as the coordinating site.

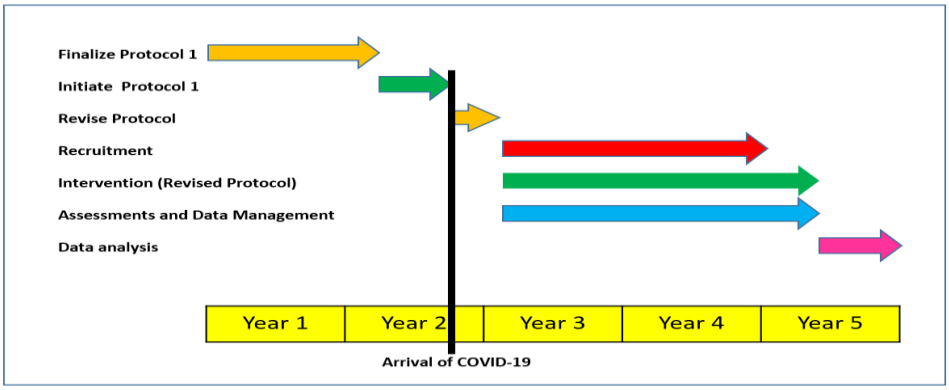
5.0 Study Timelines

- *Duration of an individual subject's participation in the study:*
  Each participant's participation in the study will last between approximately 26-52 weeks, depending on their time of enrollment into the study. The goal will be for as many participants to reach 52 weeks as the time of the study allows. Starting during inpatient hospitalization or within 90 days after an acute event and following the participants for approximately 26-52 weeks from enrollment.

- *The duration anticipated to enroll all study subjects:*
  We anticipate that we will enroll all study subjects over approximately 24 months.

- *The estimated date for the investigators to complete this study (complete primary analyses):*
  We anticipate that we will complete data collection over approximately 52 months as indicated in the study timeline below.

Study Timeline



6.0 Study Endpoints

6.1 Primary and secondary study endpoints.

All eligible and consenting patients will undergo a standard battery of assessments at baseline and after approximately 3, 6, and 12 months (12 months as the study length allows). Assessors will be blinded regarding each patient's group assignment.

Aim 1: to test relative benefits of the MACRO vs. SOC arms, comparing (a) differences in the AM-PAC CAT Basic Mobility Domain (primary outcome; primary endpoint 3 months), as well as (b) complementary functional/qualitative metrics accelerometry, AM-PAC CAT Daily Activity Scale, depression, frailty, self-efficacy, and quality of life); (c) differences in participation, and adherence; (d) readmissions and hospitalization.

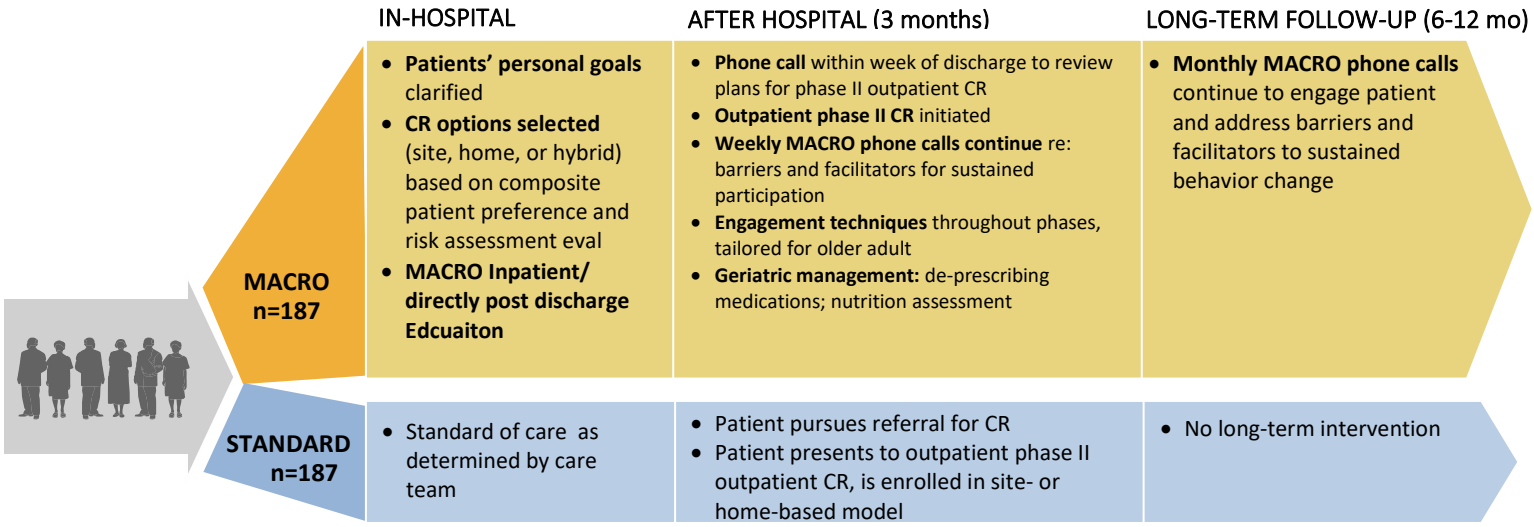
In Aim 2, assessments in physical activity (accelerometry); AM-PAC CAT Daily Activity Domain; depression; frailty; self-efficacy; and quality of life will be repeated at approximately 6 and 12 months (12 months as the study length allows) to evaluate longer term impact of the MACRO intervention vs. SOC.

In Aim 3, moderator analyses will examine characteristics of patients to identify those most likely to benefit from a MACRO intervention.

7.0 Procedures Involved

7.1 Study design.

Overview and summary of design: This is a pragmatic randomized controlled trial (RCT) of 374 older adults, with 40 subjects at the University of Pittsburgh, eligible for CR: hospitalized adults aged ≥70 years with a primary diagnosis of AMI/ACS, stable IHD, CABG, PCI, valvular heart disease (valve replacements or repairs for aortic stenosis or mitral regurgitation), PAD or HF. Patients who consent to participate will be randomly assigned to MACRO or SOC arms (which may include CR at the discretion of the providers) (Figure below). In the MACRO arm, patients will benefit from personalized engagement and CR will be explicitly facilitated, enhanced, tailored to patients' preferences and needs, and utilizing a flexible range of options (site-, home, or hybrid). In comparison, SOC provides no specialized engagement, and no programmatic facilitation, enhancement, customization, or deliberate flexibility in how care is provided.



A. Data collection overview

B. Table 1 shows outcome measures planned at each time point.

Table 1. Data Collection Plan

Study Measure	*Baseline*	*3, 6, 12 months*
Risk assessment	*X*	
AM-PAC CAT Basic Mobility Domain (primary outcome)	*X*	*X*
Accelerometer	*X*	*X*
AM-PAC CAT Daily Activity Domain	*X*	*X*
3 Day Food Record (not at WU site)	*X*	*X*
Questionnaires	*X*	*X*
CR adherence/attendance		*X*
Reduced falls, medication burden, readmissions and hospitalization	*X*	*X*

7.2 Research procedures.

Assessments
Assessments will occur at some or all of the following time points: baseline (while inpatient or up to approximately 90 days following an acute event), and 3, 6, 12 months (12 months as study length allows) post-randomization. Assessments can be completed in-person (at facility), by telephone or video call.
Assessments are outlined below:

A. **Cognitive function.** Short Blessed (score ≥13) will be used as an initial screening tool to rule-out severe cognitive impairment.

B. **Depression:** Patient Health Questionnaire 9-item (PHQ-9). Older adults eligible for CR have high rates of depressive symptoms that amplifies vulnerability to disability.[12, 13] Mitigating depressive symptoms is an important rehabilitation outcome. The PHQ-9 is a simple, pragmatic instrument that is well-validated and responsive to change. A score of 10 or greater indicates depression symptoms.[14] For all patients with PHQ-9 ≥10 who are not receiving treatment for their depression already, we will consult Dr. Lenze and also notify their primary provider (as needed) to enable follow-up and greater safety. If a participant expresses or demonstrates suicidal ideation, standard of policy of the local hospital for suicide risk will also be followed.

C. **Readiness for Change:** Interventions like CR that require active engagement by participants are often dependent on the participant's willingness to adopt new activities, habits and routines.[15] The TTM is a behavioral framework for understanding readiness for change through 5 change-stages: (1) precontemplation, (2) contemplation, (3) preparation, (4) action, (5) maintenance. In studies examining patient-centered interventions with community-dwelling older adults, increased readiness for change was associated with a 62% greater likelihood of goal attainment.[16]

D. **AM-PAC-CAT:** The AM-PAC is an activity limitations measure.[17] This measure is picked as an important complement physical assessment measures both as a self-reported index, and because it clarifies relative degrees of capacity amidst the heterogeneity anticipated in this population (i.e., frail

to robust). AM-PAC allows for the examination of perceived difficulty and level of assistance/limitations in 3 domains – Basic Mobility **(primary outcome)**, Daily Activity, and Applied Cognition, building on Item Response Theory (IRT).[18] AM-PAC- combines items from existing instruments into one scale, and ranks them according to level of difficulty for each of the 3 domains. IRT assumes that all items within a domain measure a single concept and are independent. In this study the Basic Mobility domain will be the primary outcome, and the Daily Activity domain will be one of the secondary outcomes.

E. **Self-efficacy:** Higher self-efficacy correlates to greater capacity and duration for physical activity and independence.[19-21] For this study we rely on the 13-item self-efficacy scale developed by Sullivan, et al.[22]

F. **Quality of Life (QoL):** RAND-12 is a 12-item scale developed to evaluate QOL.

G. **Falls:** Falls are a common, deleterious, and expensive aspect of aging which may be preventable via the tenets of MACRO such as good transitional care, age-appropriate exercise, and de-prescribing. We will measure falls as follows: at baseline, we will ask, "Have you had any falls in the past 3 months?" In follow-up assessments, we will ask about interim falls, as well as their severity (e.g., if they caused injury).

H. **Deprescribing-Eligible Medications (DEMs):** DEMs are medications that are potentially deleterious for participants. These medications are pre-identified, based in part on the Beers Criteria[23] and in part based on CR-specific risks of falls.

I. **Readmissions:** At follow-up assessments, we will ascertain whether the participant had any hospital admissions or other care (e.g., ER visits).

J. **Institutionalization:** At follow-up assessments, we will ascertain whether the participant required a brief or long-term institutionalization (e.g., Assisted Living, Skilled Nursing Facility [SNF] or inpatient rehabilitation).

K. **Physical activity.** Physical activity will be measured in all participants at each assessment for approximately 7-10 days using the ActiGraph accelerometer. Participants are asked to wear the ActiGraph on their wrist for 7-10 days, removing it only for times when the arm will be submerged in water for long periods of time like swimming. After 7-10 days, participants will mail the accelerometer back to the study team in a stamped, pre-addressed envelope provided to them at their study visit, or they will bring it with them to their next scheduled visit. We may also contact participants by telephone to ensure monitors are returned.

L. **Adherence to the cardiac rehabilitation program.** An assessment of the total number of CR sessions participants complete will be tracked via telephone calls, collection of data from the onsite cardiac rehabilitation programs, and/or self-report by participants at the completion of the study.

M. **Risk Assessment**. The aggregate risk of each participant will be assessed at baseline. We will assess risk across three domains: medical, functional, and psychosocial. An assignment of high, moderate, or low risk will be determined using the participants' scores on various baseline assessments.

N. **Duke Activity Status Index (DASI)** is a 12-item scale that has been validated in cardiac patients against peak VO_2 and has been demonstrated to be a reliable and responsive tool to quantify physical activity in daily living.[24]

O. **FRAIL Scale.** A five-item scale frailty assessment that assesses Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight that can be administered over the phone.[25]

P. **Rapid Estimate of Adult Literacy (REALM-SF). (optional as now contingent on COVID-19 risk)** Will be utilized to evaluate health literacy on all participants.

Q. **Nutrition:** Will be assessed with the Rapid Eating Assessment for Participants short (REAP-S)[26] (to be collected at all sites) and a 3-day food record (not collected at WU site). REAP-S is a 16-item questionnaire to assess eating habits for patients. A 3-day food record allows will also be collected to assess quantities of specific food groups (such as protein).

MACRO Intervention

Early Contact. MACRO study staff will continue to monitor inpatient participants electronic medical record charts for consults to PT/OT/CR. Education will be provided over the phone or in person to enhance the transition to home and to facilitate transition to outpatient CR. The rationale for CR will be explained and the shared decision making between the patient and providers will be emphasized.

Risk Determination. Aggregate risk assessment will be completed on each participant (both MACRO intervention and controls) with methods that integrate baseline study indices across three domains: medical, functional, and psychosocial. In the MACRO Intervention group only, these risk assessment scores will be used as a means to inform coaches of broad patient challenges that need to be addressed with CR care, as parts of site-, hybrid- and home-based options.

MACRO Intervention arm transitional care: The MACRO Intervention includes therapeutic reinforcements in the days after discharge/enrollment. When feasible, home calls start the week of discharge/enrollment, study staff will contact the participant approximately once each week (intent to treat) to address questions and to encourage the patient to continue the chosen CR option (site-, home-, or hybrid). Phone calls will continue throughout the phase II CR period to help ensure adherence and as recovery evolves.

Our methods for maintaining care and observation throughout transitions (including to skilled term nursing facility [SNFs] or rehab) were developed at the VAPHS and include (1) Establishing rapport with potential participants and their families; (2) Collecting information for several different methods of contact to ensure close communication over the duration of the study; (3) Phone calls with participants intermittently while they are at SNF or inpatient rehab; (4) sending reminders to the participants and their family members that the team will be calling them; (5) Verification of discharge plan at SNF/rehab discharge and confirmation that alternate contact information is up-to-date.[27]

Patients in the MACRO Intervention arm will be encouraged to participate in outpatient phase 2 Clinical CR (site-, home- or hybrid-based options)

Site-based Clinical CR: MACRO Intervention participants may be enrolled in outpatient site-based CR. In addition to the commitments and benefits of that program, participants will also receive weekly MACRO phone calls that reinforce complementary MACRO-based priorities. The emphasis of the calls is to

reinforce the site-based programs, and to also better facilitate the goal of transitioning from site-based CR to management the participant can achieve independently at home..

Home-based Clinical CR: MACRO Intervention participants may be enrolled in home-based CR. While home-based CR will vary with each site's clinical program and even within each program over time, minimal standards of home-based CR for MACRO will include at least weekly contact by qualified personnel, with implementation of a curriculum that offers requisite components of exercise training, education, support, and linkage to dietary consultation when indicated.

In addition to the commitments and benefits of the home-based program, participants in the MACRO intervention arm will also receive weekly MACRO phone calls that reinforce complementary MACRO-based priorities. The emphasis of the calls is to reinforce the home-based programs.

Hybrid-based Clinical CR: MACRO Intervention patients may also be enrolled in hybrid-based CR**.** Hybrid CR starts with site-based care, but then transitions to home-based care as the patient and clinicians feel suitable. The transition may be triggered by evolving medical stability, growing self-confidence, or other factors which impact on each patient's capacity for home-based CR. The time required for this transition will vary between individuals.

In addition to the commitments and benefits of the hybrid program, participants in the MACRO intervention arm will also receive weekly MACRO phone calls that reinforce complementary MACRO-based priorities. The emphasis of the calls is to reinforce hybrid CR.

Responding to patients' goals and needs: The MACRO Intervention arm tailors care to each participant in two ways, matching care to (1) the participant's personal preferences as part of Enhanced Medical Rehabilitation (EMR) goal setting and motivational; and (2) elements of risk that are detected as part of their comprehensive risk profile (that includes medical, physical, and psychosocial domains). The underlying premise is that each patient requires a personalized approach to integrate preferences and risks. MACRO's flexibility is an essential aspect of this management. The MACRO intervention, for example, emphasizes seated activities for patients with risks of falls. The MACRO intervention also organizes family supports, repetitive learning strategies, and community activity resources for participants with learning impairments. The MACRO intervention emphasizes strength, balance, and nutrition for participants who are frail.

CDC Check for Safety Check list:
Participants in the MACRO Intervention arm may receive a Home Fall Prevention Checklist for Older Adults. This check list will be utilized to provide the participant the opportunity to be better informed about safety. The check list may be sent when direct home assessments are not completed.

MACRO De-Prescribing: All participants in MACRO will have their medications reviewed to identify DEMS (deprescribing eligible medications). DEMs worsen functional recovery, impair cognitive function, and increase medical risks (falls, bleeding).[31] For participants in the MACRO Intervention arm, opportunities for de-prescribing will be reviewed and specific recommendations will be conveyed to the participant's clinician to optimize recovery (optimizing physical function, minimizing confusion, reducing falls).

Deprescribing assessments will be conducted during the baseline assessments as part of a medication review. Communication will then be initiated with the MACRO participant's primary provider. DEMs have been selected based on goals to optimize function, reduced sedation, and minimize falls.

If DEMS are deprescribed, a standardized approach of follow-up assessments will be implemented to ensure deprescription is well tolerated.

MACRO arm personalized nutrition: Older CVD patients are particularly prone to sarcopenia, frailty, and associated vulnerabilities such as exercise intolerance, falls, and poor QOL. A high-quality diet and increased protein intake have been shown to be advantageous in these vulnerable adults.[OBJ] The MACRO Intervention participants will be strongly encouraged to meet with a registered dietitian and receive dietary recommendations that will account for sarcopenia, underweight, overweight, and specific dietary restrictions associated with comorbid conditions (e.g., DM, renal disease) and medications. Nutrition education and facilitation will be optimized in MACRO. The MACRO Intervention participants will be strongly encouraged to meet with a registered dietitian and receive dietary recommendations that will account for sarcopenia, underweight, overweight, and specific dietary restrictions associated with comorbid conditions (e.g., DM, renal disease) and medications. Nutrition education and facilitation will be optimized in MACRO.

MACRO Intervention arm telephone intervention. MACRO staff will contact participants randomized to the MACRO arm approximately once each week until the completion of phase II after which approximately monthly phone calls will be completed. A subset of telephone calls will have a second MACRO staff member listening to calls to enable additional monitoring. The components of each session recorded on the checklist.

7.3 Quality Assurance

A. **Fidelity** refers to whether team members consistently perform the MACRO intervention with a high level of adherence to and competence with the intervention protocol. Low fidelity is a common and often unrecognized problem leading to "failed" intervention studies.[33] We will apply expertise from numerous intervention studies, including multi-site studies: (1) Attaining fidelity – we will train team members at each site. (2) Measuring and maintaining fidelity – Co-investigators will have regular supervisory calls with team members. Their intervention sessions may be randomly sampled by the supervisors and rated according to meeting fidelity standards. The PIs are the ultimate fidelity supervisors; they will be in regular contact with the supervisors, study coordinators, and research assistants to promptly detect and correct problems. Such training and monitoring have been successful in our recent rehabilitation studies.[34]

B. **Interventionist training and certification.** Prior to beginning the study, the research staff will be trained on the intervention. Regular telephone calls will be held with intervention research staff to discuss problem participants or challenging issues that arise in the delivery of the intervention.

C. **SOC control group.** The SOC group controls for the possibility that regular contact with the study team may improve outcomes in participants randomized to the intervention. Participants randomized to the SOC group will follow the standard hospital process and may or may not receive CR.

D. **Quality control of outcome measures.** All research study staff will be trained in each aspect of the study that they are involved in. Training will be completed by subject matter experts in the specific area within the research team. Data will be reviewed for quality control, standardization, and abnormalities in collection and will be discussed at regular meetings.

7.4 Procedures performed to lessen the probability or magnitude of risks.

In the event that in-person assessments or interventions become infeasible (e.g., COVID 19 outbreak), the researchers will carry out these study components remotely (i.e., by telephone, mail, email, Redcap, e-consent, or video call.

A. **Adequacy of protection against risks and methods to minimize potential risks.** Overview of protection against risks. Research staff is trained in each element of the study visit they will perform; including obtaining informed consent, administering questionnaires, protecting confidentiality of collected data, performing the frail assessment. Additional training will be provided as needed.

B. **Minimizing risks related to assessments.** If a participant develops symptoms such as chest discomfort, new dyspnea, new fatigue, study staff will notify hospital or facility staff, or the study cardiologist.

C. **Staff Training.** All research staff will undergo training and certification prior to working with participants and will re-certify as necessary every 12 months to ensure continued adherence to study protocol.

D. **Minimizing risk related to loss of confidentiality.** The following methods will be employed to maintain confidentiality of participants. Research staff members have completed training in the ethical conduct of human subject research, including maintaining participant confidentiality. Only study investigators and research staff will have access to the study database. Participants will be assigned a unique study identifier. Individual names will ultimately be removed from the study database and only the unique study identifier will be used to distinguish participants in the database. Data will be maintained in computer files and file cabinets to which only the study staff have access. Collected data will be used only for research purposes. Any published data will not contain any individual identifiers.

E. **Minimizing risk related to loss of confidentiality during intervention.** Participation includes a risk of loss of confidentiality regarding personal health information. However, all research staff have undergone formal human subjects training. They are trained to protect the privacy of research subject participants.

F. **Data and Safety Monitoring Board (DSMB).** The DSMB will meet approximately every six months or as decided by the DSMB. The DSMB will meet to review and approve the protocol prior to beginning data collection. They will decide on specific stopping criteria for the study. The biostatistician and data manager will work closely with the DSMB to provide reports in an acceptable format. Serious Adverse events (SAE) / Adverse events will be monitored continuously throughout the study and will be reported to the DSMB and IRB according to pre-specified requirements. SAE/AE rates and interim study results will be reviewed and discussed by the DSMB at the DSMB meetings.

7.5 Source records that will be used.

Sources of material. Primary and secondary outcome measures that will be collected for this study include the AM-PAC CAT, accelerometry, cognitive assessment, depression, frailty, IADLs, readiness for change, adherence, self-efficacy, falls, medication assessment, readmissions, institutionalization.

8.0 Data Storage

8.1 Data to be stored

Data at the active sites will be coded; meaning that a key will exist that can link the codes back to the direct subject identifiers. Each participant will be assigned a unique study ID number that can be traced back to the study participant. Data provided to the coordinating center will be de-identified.

8.2 Procedures to release data.

Only the local site PI has control over release of study data. Any investigators seeking to analyze data must contact the site PI for permission. Each request, if it occurs, will be considered on a case-by-case basis and will require obtaining IRB approval prior to releasing.

9.0 Data Management

9.1 Data analysis plan.

A. **Data management.** Data management staff will coordinate the data oversight under the direction of Dr. Perera study statistician for all sites and will utilize the insight form the University of Pittsburgh Physical Therapy Data Center for Data Management.

B. **Data Safety Monitoring Board (DSMB).**
The DSMB will also be expected to meet as needed, but not less than, every six months to provide an overall summary status report to the regulatory agencies. An emergency meeting of the DSMB may be called at any time by the Chair should participant safety questions or other unanticipated problems arise**.**

In addition, the DSMB Report addressing the following information will be submitted to the IRB at the time of continuing review annually or more often as required:

- A list of the research personnel who participated in the data and safety monitoring.
- The frequency of monitoring that took place during the renewal intervals and/or the dates that data and safety monitoring was conducted.
- A summary of cumulative data related to unanticipated problems (including adverse events) including a determination of causality and whether the risk to benefit assessment has changed.
- If appropriate, a summary of pertinent scientific literature reports, therapeutic developments, or results of related studies that may have an impact on the safety of study participants or the ethics of the research study.
- A summary of the outcome of reviews conducted to ensure subject privacy and research data confidentiality.

Final conclusions regarding changes to the anticipated benefit-to-risk assessment of the study participation and final recommendations related to continuing, changing, or terminating the study.

C. **Statistical Analyses.** *Overview*-We will perform all main analysis based on intention-to-treat philosophy following the a priori plans outlined below. All statistical analyses will be performed and overseen by the study statistician Dr. Perera using SAS® version 9 (SAS Institute, Inc., Cary, North Carolina). Participant flow will be summarized using a CONSORT diagram.[35] Data will be summarized by treatment group and time point as well as baseline to follow-up change using appropriate descriptive statistics. First, the baseline participant characteristics will be compared between the two arms. Any significant differences will be noted and accounted for as additional covariates in the sensitivity analyses. Second, main analyses to address the aims will be performed as outlined below. Confirmatory hypothesis testing will be performed using multiple imputation for missing data. Third, a set of sensitivity analyses including additional covariates and ignoring missing data will be performed to evaluate the robustness of our findings.

Baseline Comparisons-Due to the randomization scheme balanced with respect to study site and the large sample size, it is unlikely that other baseline participant characteristics will be significantly different between the arms. However, we will control for any participant characteristics that are found to be significantly different by including them as additional covariates in the sensitivity analyses. In such an event, we will not alter the primary analytic strategy to preserve its a priori nature and predictability. We will use independent samples *t*-, Wilcoxon rank sum, chi-square and Fisher's exact tests, as appropriate based on distributional properties, and continuous/categorical nature of the characteristic being compared.

Aim 1 Analysis-We will fit a series of linear mixed models[36] using the SAS® MIXED procedure with baseline to follow-up changes in continuous outcomes as the dependent variable; intervention arm (MACRO/SOC), follow-up time point (3/6/12 months) and their interaction term as the fixed effects of interest; the baseline value of the continuous outcome as a fixed effect covariate; and a participant random effect to account for multiple measurements over time from the same participant. We will appropriately construct means contrasts to estimate MACRO vs SOC at each follow-up time point. The magnitude and statistical significance at $\alpha=0.05$ of the MACRO vs SOC difference at 3 months for AM-PAC CAT Basic Mobility Domain will serve as the formal test of the primary hypothesis H1.1. If significant, we will define a meaningful responder as having at least a 2.60 point improvement in AM-PAC CAT Basic Mobility Domain[17] over 3 months, compute percentage of responders in both arms, and conclude a number-needed-to-treat (NNT) as the reciprocal of the difference in percentages. We will employ the same analytic strategy described above for each of our secondary continuous outcomes such as physical activity, depression, frailty, self-efficacy and quality of life (H1.2). For the secondary outcomes measured only once at 3 months such as participation, adherence and satisfaction (H1.3), we will consider using Wilcoxon rank sum, chi-square and Fisher's exact tests to make between-intervention comparisons, depending on the categorical/ordinal/interval nature of the outcomes and their propensity for ill-behaved distributional properties. For count outcomes such as falls, number of medications, readmissions and hospitalizations in H1.4, we will fit a series of negative binomial regression models[37] with the count outcome as the dependent variable; exposure time for the counts as an offset; a log link function; and intervention arm as the main independent factor of interest; and a marker of history of the outcome at baseline as a covariate MACRO vs SOC incident rate ratio and its statistical significance will serve as tests of H1.4.

Aim 2 Analysis-In the linear mixed models described above for H1.1 and H1.2, we will examine the between-intervention means contrasts at 6- and 12-months. The magnitude and statistical significance of the MACRO vs SOC arm differences at 6 and 12 months will serve as the formal test of the hypothesis H2.1.

Aim 3 Analysis- We will examine characteristics of patients likely to reap the greatest benefits from MACRO compared to SOC arms and will be accomplished through exploratory subgroup analyses. We will examine subgroups based on baseline AM-PAC CAT Basic Mobility Scale, frailty status, cognitive function, and readiness for change. Specifically, for each subgroup definition considered, we will add subgroup and subgroup × intervention group interaction terms to the models used in Aims 1 and 2. If the interaction terms are statistically significant, we will make subgroup-specific between-intervention comparisons.[38]

Our second avenue of exploration would be to delineate characteristics of patients most/least likely to reap benefits from the MACRO intervention. Specifically, we will only use the data from the MACRO arm, and define a meaningful responder as having a 3-month improvement of at least 2.60 points in AM-PAC CAT Basic Mobility Scale. First, we will compare the baseline characteristics of

responders and non-responders using methods described above. Second, we will fit logistic regression models with responder status (yes/no) as the dependent variable, and each of the baseline characteristics, one-at-a-time, as the sole independent variable to identify which factors a likely to be relevant. Third, we will fit a multivariable logistic regression model with all relevant baseline characteristics as independent variables, and a forward selection strategy to potentially identify a parsimonious collection of relevant baseline characteristics predictive of likelihood of benefit. Finally, to better accommodate non-linear associations and interaction effects among baseline characteristics, we will consider a classification tree model or CART.[39]

Missing Data-The best approach for handling missing data is prevention, and our clinical trials have had a low missingness rate. We will clearly document missing data and reasons in the CONSORT diagram and compare those with missing data to complete data at the follow-up assessments using the same methods outlined under *Baseline Comparisons* subsection above. We will use methods such as multiple imputation which consider the uncertainty involved in imputing missing data.[40-42] Multiple imputation is arguably the best method to account for missing data under the ignorable or missing-at-random (MAR) assumption, and mitigates bias even when missing data is non-ignorable.[43] Specifically, we will generate M=5 imputed values for each missing value, analyze the 5 datasets as though complete, and finally combine the results appropriately so that they reflect the uncertainty involved in imputation. SAS® MI and MIANALYZE procedures will be used. Other approaches to missing data will also be considered in sensitivity analyses.

Sensitivity Analyses-We will perform sensitivity analyses to examine the robustness of our results against various assumptions, such as fitting zero-inflated models[44] or using dichotomous (any/none) operational definitions and logistic regression models. In addition, if analyses of residuals from the linear mixed models show violations of statistical assumptions, we will consider fitting models after Box-Cox transforming the continuous variables to make them approximately conform to a normal distribution.[45]

D. **Sample Size and Power.**

Sample Size Justification. We base our sample size on published data, published statistical methods, and commercially available software (SAS® POWER procedure; SAS Institute, Inc., Cary, North Carolina). Between-subject standard deviation of the baseline to follow-up change in the primary outcome AM-PAC CAT Basic Mobility Scale is approximately 7.97 in rehabilitation outpatients.[17] We consider 2.60 points a minimally clinically important difference based on MDC_{68} [17, 46]. We plan to randomize 187+187=374 participants, anticipating 149+149 completers assuming a conservative 80% retention rate. We can detect a between treatment arm difference of 2.60 points in AM-PAC CAT Basic Mobility Scale with 80% statistical power in a two-tailed test at $\alpha=0.05$.[47-50] This difference is smaller than the actual observed changes previously reported, indicating ample statistical sensitivity. The logistic regression model proposed in Aim 3 requires a minimum of about 5-10 events per variable, and assuming a half in the MACRO group responds, we would be able to fit a multivariable model with at least 15 variables. Thus, we are confident of the adequacy of sample size to address all aims.

9.2 Steps to secure data to maintain confidentiality during storage, use, and transmission.

All research staff must complete training in protection of subject privacy and prevention of disclosure of identifying information.

All data collection forms are maintained in a secure office space.

Our study databases are maintained in locked computer files or on secure hard drives that are password protected; to which only authorized staff have access. A study manager must provide permission for programmers and research assistants to access study databases.

A study identification number will be assigned to each participant. This identification number will be randomly generated and will only be connected to patient identifiers by a master list maintained at each site.

9.3 Describe any procedures that will be used for quality control of collected data.
Quality Control. All study staff will undergo certification training prior to the beginning of the study. Every month data checks will occur to check accuracy of the data collection. Additionally, to ensure uniformity of sites there may be site visits and on-site trainings for staff.

10.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Serious adverse events (SAE) and Adverse events (AE) will be reported to the DSMB following the DSMB charter guidelines. The DSMB will have the ability to stop the study at any time if there are concerns about safety. SAE will also be reported to each active site's IRB following the provisions required for that site.

- To provide for more complete assessment of the possible impact of COVID-19 on MACRO, the unblinded study physician and study coordinator at each site will work immediately and directly with the study statistician if they have any concerns that an AE/SAE is attributable to COVID-19. This will prompt an expedited report to the DSMB and NIA.

  The AE/SAE SOP will be updated accordingly.

11.0 Withdrawal of Subjects

Participants may withdraw from the research at any time. If participants decide to leave the research, they should contact the site PI at their active site.

If participants stop being in the research, data already collected may not be removed from the study database. Participant will be asked whether the investigator can collect data from their routine medical care. If the subject agrees, this data will be handled the same as research data.

12.0 Risks to Subjects

12.1 Foreseeable risks

A. **Risks associated with the MACRO home-based and hybrid-based CR program.**
Participants will be increasing exercise and physical activity. Such activity may be associated with muscle soreness, musculoskeletal irritation, shortness of breath, fatigue, light-headedness, chest discomfort, or nausea. Physical activity and exercise may also be associated with an increased risk of a cardiovascular event, such as a heart attack, cardiac arrest, dangerous arrhythmia, or stroke. However, MACRO participants will always be approved for participation by their personal clinician to best ensure they are sufficiently stable and such that risks are minimized.

Participants participating in CR (site- hybrid, or home-based models) will not participate in progressive exercise until a physician deems it appropriate.

B. **MACRO intervention**

CDC CHECK FOR SAFETY; A Home Fall Prevention Checklist for Older Adults will be mailed to participants and education will be provided based on participant questions. If there are concerns raised by this the PCP will be contacted and a clinical safety assessment will be requested on the participants behalf.

C. **Cognitive and depression assessment.** The PHQ9 and Short Blessed (screening) assessments. Each assessment will be self-completed by participants, and they will have the option to skip questions if they feel uncomfortable answering. Additionally, staff will be trained in addressing questions and will have direct contact with clinical staff to handle more complex occurrences following each hospitals outpatient standard operation procedures for increased behavioral health assistance.

D. **Risks associated with questionnaire administration**. Participation includes a risk of loss of confidentiality regarding personal health information. However, all research staff have undergone formal human subjects training to reduce this risk. Research staff are trained to protect the privacy of research subject participants. Burdens associated with questionnaires may be exacerbated by the challenge of administering these tools over the phone.

E. **Accelerometry assessment**: Participants may wear an ActiGraph which is a watch like device that goes on your wrist for 7-10 days there is the small chance it may cause a rash or irritation of the skin but no more than wearing a regular watch.

12.2 If applicable, indicate which procedures may have risks to* the *subjects that are currently unforeseeable.

There may be risks that are currently not foreseeable as part of the study assessment and intervention.

13.0 Potential Benefits to Subjects

13.1 The potential benefits that individual subjects may experience from taking part in the research.

A. **Potential benefits of the proposed research.** Participation in the proposed research may or may not provide a direct benefit to participants in this research but will enhance the area of medicine on knowledge related to the impact of the intervention at improving patient care. Additionally, this research involves an intervention that holds the potential for direct individual benefit. The risk is justified by the extent of potential benefit to the involved adults, which includes the possibility of improved cardiorespiratory fitness (CRF), efficiency, and PA. These data are important for the rising population of older adults who are prone to sedentariness and detrimental health effects.

B. **Clinical practice guidelines:** Recommends CR for all patients post-acute cardiovascular event, however CR is drastically underutilized across the Unitized States and even more so by the growing number of older adults. CR is a structured program that provides exercise and education for

reduction of future cardiovascular events, and evidence has shown that CR increases life expectancy and decreases long term hospital cost. CR programs often require driving to facilities with limited scheduled and costs associated with each visit which can create barriers for many patients. Additionally, many patients are not told about the availability of CR or the importance of CR is not emphasized at the time of the acute cardiac event. MACRO directly addresses this issue by creating the facilitation to CR program.

C. **Importance of knowledge to be gained:** MACRO responds to a critical gap in CVD management by marrying CR principles with geriatric risk modifying strategies in an intentional and flexible treatment approach that can be generalizable. MACRO is designed to optimize accessibility and effectiveness, and to augment the potential for recovery from CVD events that are highly prevalent and otherwise prognostically dire. MACRO constitutes an important advance in geriatric cardiology wherein the conventional approach to CVD care is transmuted and enriched by linking cardiovascular management to the broader complexity of aging**.**

14.0 Sharing of Results with Subjects

Participants will not be provided with any study results unless there is a clinically significant event that occurs as part of the research project.

15.0 Setting

Visits will be completed in-person while inpatient and outpatient visits will be completed via telephone or

video call at each of the active sites.

16.0 Recruitment Methods

16.1 When, where, and how potential subjects will be recruited.

A. **Recruitment methods**

A variety of mechanisms will be used to recruit participants for this protocol. Participants eligible for cardiac rehabilitation will be identified from inpatient and outpatient admissions by reviewing the electronic medical records, daily admission lists, cardiology consults and clinic, direct referrals, pre-operative lists, and discharge lists. Study team recruiter will request bedside nurse to ask patient if it is okay to approach and to explain study. Those interested in participating further will be provided the study brochure and study contact information or the option to complete the initial screening in person. Interested discharged patients will be approached after discharge if they are unable to be seen by a study team member during their stay.

B. **Advertisements**

An approved study flier and recruitment brochure will be placed in key places and/or be distributed to physician offices, related clinics, or on other occasions/venues that present as an opportunity to recruit (e.g., a PI speaking engagement). Potential participants can self-refer by contacting the study staff via a telephone number/email address that is provided on these advertisements. With subject permission, they will be screened on the phone to make a preliminary assessment of eligibility. We will obtain permission to access their medical records in the UPMC database or request records from their provider as needed to further document eligibility.

Advertisement, such as on radio, television, internet or social media, print copy in newspapers, or bus signs may also be utilized depending on recruitment rates.

16.2 Amount, timing, and method of any payments to subjects.

Subject Reimbursement

The participant will receive $20 for each of the assessments that s/he undergoes and $10 per Actigraph return up to $120. If the participant withdraws from the study, s/he may still retain payment for the portions of the study that s/he completed. Participants may be reimbursed based on mileage.

17.0 Number of Subjects

Recruitment.

We will randomize approximately 374 participants, approximately 40 at the University of Pittsburgh over approximately 24-months, allowing for a 20% drop-out at 52-week follow-up.

18.0 Provisions to Protect the Privacy Interests of Subjects

18.1 Steps that will be taken to protect subjects' privacy interests and to make the subjects feel at ease with the research situation.

Questionnaires and assessments will be administered by telephone calls/video calls and/or appropriate space based on the activity by a trained and certified research staff member. All information collected as part of the study will be stored in double locked locations or on secure access drive in which only study staff have access in accordance with each site's regulation. Only de-identified data will be provided to coordinating center.

19.0 Consent Process

Participants must provide informed consent. The information about this study will be given to the subject in language understandable to them. A trained member of the research team will present the study. They will verbally present a general outline of the research plan, including inclusion and exclusion criteria, to the prospective participant. The consent form, outlining the design of the study, will include the risks and benefits of participating, and will be reviewed. The consenting member of the research team will answer any questions. Prospective participants may take as much time as required to make an informed decision. Written informed consent will be obtained from each participant and the research team member prior to performing any research study procedures. Site PI or another study investigator are also available to answer any questions that participants may have about the research.

Non-English-Speaking Subjects

Potential participants who do not speak English will not be eligible for study participation.

Subjects who are not yet adults (infants, children, teenagers)

Children will not be involved in this research.

Cognitively Impaired Adults

Participants who are cognitively impaired will not be eligible.

Consent will be required from all study participants.

Participants who cannot provide informed consent are not eligible for participation.

20.0 References

1. McMahon SR, Ades PA, Thompson PD. The role of cardiac rehabilitation in patients with heart disease. *Trends in cardiovascular medicine.* 2017;27(6):420-425.
2. Schopfer DW, Forman DE. Cardiac Rehabilitation in Older Adults. *The Canadian journal of cardiology.* 2016;32(9):1088-1096.
3. Ruano-Ravina A, Pena-Gil C, Abu-Assi E, et al. Participation and adherence to cardiac rehabilitation programs. A systematic review. *International journal of cardiology.* 2016;223:436-443.
4. Anderson L, Sharp GA, Norton RJ, et al. Home-based versus center-based cardiac rehabilitation. *The Cochrane database of systematic reviews.* 2017;6:Cd007130.
5. Hamm LF, Kavanagh T, Campbell RB, et al. Timeline for peak improvements during 52 weeks of outpatient cardiac rehabilitation. *Journal of cardiopulmonary rehabilitation.* 2004;24(6):374-380; quiz 381-372.
6. Forman DE, LaFond K, Panch T, Allsup K, Manning K, Sattelmair J. Utility and efficacy of a smartphone application to enhance the learning and behavior goals of traditional cardiac rehabilitation: a feasibility study. *Journal of cardiopulmonary rehabilitation and prevention.* 2014;34(5):327-334.
7. Forman DE, Arena R, Boxer R, et al. Prioritizing Functional Capacity as a Principal End Point for Therapies Oriented to Older Adults with Cardiovascular Disease: A Scientific Statement for Healthcare Professionals from the American Heart Association. *Circulation.* 2017;135(16): e894-e918.
8. Forman DE, Rich MW, Alexander KP, et al. Cardiac care for older adults. Time for a new paradigm. *Journal of the American College of Cardiology.* 2011;57(18):1801-1810.
9. Covinsky KE, Pierluissi E, Johnston CB. Hospitalization-associated disability: "She was probably able to ambulate, but I'm not sure". *Jama.* 2011;306(16):1782-1793.
10. Guidelines for Cardiac Rehabilitation and Secondary Prevention Programs. Medical Evaluation and Exercise Testing. *5th Edition with Web Resource Chapter 6.*
11. Lenze EJ, Host HH, Hildebrand MW, et al. Enhanced medical rehabilitation increases therapy intensity and engagement and improves functional outcomes in postacute rehabilitation of older adults: a randomizedcontrolled trial. *Journal of the American Medical Directors Association.* 2012;13(8):708-712
12. Fredman L, Hawkes WG, Black S, Bertrand RM, Magaziner J. Elderly patients with hip fracture with positive affect have better functional recovery over 2 years. *Journal of the American Geriatrics Society.* 2006;54(7):1074-1081.
13. Lequerica AH, Donnell CS, Tate DG. Patient engagement in rehabilitation therapy: physical and occupational therapist impressions. *Disability and rehabilitation.* 2009;31(9):753-760.
14. Lowe B, Unutzer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the patient health questionnaire-9. *Medical care.* 2004;42(12):1194-1201.
15. Rasmusson K, Flattery M, Baas LS. American Association of Heart Failure Nurses position paper on educating patients with heart failure. *Heart & lung : the journal of critical care.* 2015;44(2):173-177.
16. Waldersen BW, Wolff JL, Roberts L, Bridges AE, Gitlin LN, Szanton SL. Functional Goals and Predictors of Their Attainment in Low-Income Community-Dwelling Older Adults. *Archives of physical medicine and rehabilitation.* 2017;98(5):896-903.
17. Jette AM, Haley SM, Tao W, et al. Prospective evaluation of the AM-PAC-CAT in outpatient rehabilitation settings. *Physical therapy.* 2007;87(4):385-398.
18. Chakravarty EF, Bjorner JB, Fries JF. Improving patient reported outcomes using item response theory and computerized adaptive testing. *The Journal of rheumatology.* 2007;34(6):1426-1431.
19. Bandura A. Self-efficacy: The exercise of control. *New York: Freeman.* 1997.

20. Sol BG, van der Graaf Y, van Petersen R, Visseren FL. The effect of self-efficacy on cardiovascular lifestyle. *European journal of cardiovascular nursing: journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology.* 2011;10(3):180-186.
21. McAuley E, Blissmer B. Self-efficacy determinants and consequences of physical activity. *Exercise and sport sciences reviews.* 2000;28(2):85-88.
22. Sullivan MD, LaCroix AZ, Russo J, Katon WJ. Self-efficacy and self-reported functional status in coronary heart disease: a six-month prospective study. *Psychosomatic medicine.* 1998;60(4):473-478.
23. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *Journal of the American Geriatrics Society.* 2015;63(11):2227-2246.
24. Hall AM, Ferreira PH, Maher CG, Latimer J, Ferreira ML. The influence of the therapist-patient relationship on treatment outcome in physical rehabilitation: a systematic review. *Physical therapy.* 2010;90(8):1099-1110.
25. Morley , J. E. , Malmstrom , T. , & Miller , D. (2012). A simple Frailty Questionnaire (FRAIL) predicts outcomes in middle aged African Americans . The Journal of Nutrition, Health & Aging , 16 (7), 601 – 608 .American Occupational Therapy Association (2017). Home Safety and Accessibility Assessments. 2017.
26. Segal-Isaacson CJ, Wylie-Rosett J, Gans KM. Validation of the Short Dietary Assessment Questionnaire: The Rapid Easting and Activity Assessment for Participants Short Version (REAP-S). Diabetes Educ Actions. Sep-Oct 2004;30(5):774, 776, 778.
27. Skidmore ER, Dawson DR, Butters MA, et al. Strategy Training Shows Promise for Addressing Disability in the First 6 Months After Stroke. *Neurorehabilitation and neural repair.* 2015;29(7):668-676.
28. American Occupational Therapy Association (2017). Home Safety and Accessibility Assessments. . 2017.
29. Chiu T, Oliver, R., Ascott, P., Choo., L. C., Davis, T., Gaya, A., Letts, L. Safety Assessment of Functional and the Environment for Rehabilitation-Health Outcome Measurement and Evaluation (SAFER-HOME). *Toronto, ON: COTA Health.* 2006(Version 3 manual).
30. Chiu T, & Oliver, R. Factor analysis and construct validity of the SAFER-HOME. *Occupational Therapy Journal of Research.* 2006;6:132-142.
31. Dahabreh IJ, Hayward R, Kent DM. Using group data to treat individuals: understanding heterogeneous treatment effects in the age of precision medicine and patient-centred evidence. *International journal of epidemiology.* 2016;45(6):2184-2193.
32. Landi F, Calvani R, Tosato M, et al. Protein Intake and Muscle Health in Old Age: From Biological Plausibility to Clinical Evidence. *Nutrients.* 2016;8(5).
33. Hildebrand MW, Host HH, Binder EF, et al. Measuring treatment fidelity in a rehabilitation intervention study. *American journal of physical medicine & rehabilitation.* 2012;91(8):715-724.
34. Bland MD, Birkenmeier RL, Barco P, Lenard E, Lang CE, Lenze EJ. Enhanced Medical Rehabilitation: Effectiveness of a clinical training model. *NeuroRehabilitation.* 2016;39(4):481-498.
35. Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Jama.* 2001;285(15):1987-1991.
36. Littell RC MG, Stroup WW, Wolfinger RD, Schabenberger O. Cary. *SAS® for Mixed Models.* 2006;Second Edition(North Carolina: SAS Institute, Inc).
37. Hilbe JM. Negative Binomial Regression. *New York: Cambridge University Press.* 2007.
38. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine--reporting of subgroup analyses in clinical trials. *The New England journal of medicine.* 2007;357(21):2189-2194.
39. Breiman L FJ, Stone CJ, Olshen RA. Classification and Regression Trees. *CRC Press.* 1984.
40. Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. *The New England journal of medicine.* 2012;367(14):1355-1360.
41. Rubin. Multiple imputation for nonresponse in surveys. *New York;Wiley.* 1987.
42. Rubin. Multiple imputation after 18+ years. . *ournal of the American Statistical Association* 1996;91:473-489.

43. Graham JW HS, Donaldson SL, MacKinnon DP, Schafer JL.. Analysis with missing data in prevention research. In: Bryant K, Windle M, West SG eds. The Science of Prevention: Methodological Advances from Alcohol and Substance Abuse Research. *American Psychological Association.* 1997.
44. Lambert D. Zero-Inflated Poisson Regression Models with an Application to Defects in Manufacturing. *Technometrics.* 1992;34:1-14.
45. Box GEP CD. An Analysis of Transformations. *Journal of the Royal Statistical Society Series B-Statistical Methodology* 1964;26:211-252.
46. Wright A, Hannon J, Hegedus EJ, Kavchak AE. Clinimetrics corner: a closer look at the minimal clinically important difference (MCID). J Man Manip Ther. 2012 Aug; 20(3): 160–166.
47. Julious SA. *Sample Sizes for Clinical Trials.* Boca Raton, FL.: Chapman & Hall/CRC.; 2010.
48. Chow S-C, Shao, J., and Wang, H. . *Sample Size Calculations in Clinical Research (Second Edition).* Boca Raton, FL.: Chapman & Hall/CRC; 2008.
49. Machin D, Campbell, M., Fayers, P., and Pinol, A. . *Sample Size Tables for Clinical Studies.* 2nd Edition ed. Malden, MA.: Blackwell Science; 1997.
50. Zar JH. *Biostatistical Analysis.* 2nd Edition ed. Englewood Cliffs, New Jersey.: Prentice-Hall; 1984.