11. SPECIFIC AIMS

The cardiovascular (CV) consequer growing T2D epidemic pose a major social and economic burden to society. Increasing physical a associated with reduced CV morbidity and mortality in people with T2D. Physical activity levels a very low in people with T2D compared to similarly overweight nondiabetic people.[1] Thus, increasing physical activity in people with T2D remains a critical CV health priority. In prior RCTs of behavioral interventions in people with T2D,[2] physical activity levels increased in response to behavior change tools such as goal setting and motivational interviewing to overcome participant barriers. Integrating effective behavior change tools into clinical practice would provide a favorably broad reach. However, prior behavioral interventions were time and resource-intensive and such interventions may not be practical in **clinical practice settings**.[2] To move towards integrating physical activity interventions into clinical practice, we need behavioral interventions that are simple yet effective.[3,4]

We have pilot data to suggest that trained clinical staff can successfully deliver a behavioral physical activity intervention. Also, our clinic and others[5] have implemented valid methods that can identify sedentary patients who could benefit from treatment. In this grant application, we propose an innovative approach that fully integrates both trial recruitment standards (i.e., assessing participant inclusion/exclusion criteria) and intervention delivery methods into clinical practice settings. The chief advantages of the proposed work are: 1) using clinical staff and clinical processes to include appropriate patients who may be safely active — true clinical integration; 2) adding reimbursable in-person treatment visits with a physician assistant who coordinates treatment with clinic health promotion counselors — enhances safety and improves translational potential.

My K23 research objective is to pilot-test the feasibility and effectiveness of an evidence-based physical activity counseling intervention that is tailored to patient barriers and facilitators. My rationale is that the proposed research could shift the paradigm of physical activity counseling in primary care by developing an intervention that utilizes evidence-based behavior change methods but is brief enough to be widely implemented in clinical practice. We are powered to detect differences in physical activity and we also expect improvement in our secondary outcomes related to physical activity and physical function.

My focus previously was on lab-based supervised exercise to increase physical activity in adults with T2D and normal physical function — this has evolved to focus on translational research in primary care to increase physical activity in adults with T2D who often have physical function limitations. Therefore, my K23 training goals are to acquire advanced skills in: 1) functional assessments and rehabilitation of adults with functional limitations and 2) implementation science methods. Meeting my K23 goals for training and research will position me to lead the way to develop, test and implement clinical treatments to improve health and function for adults with T2D who are at high risk of cardiovascular disease.

Purpose: Conduct a randomized controlled trial with 1:1 patient-level randomization to an evidence-based physical activity program intervention vs. usual care in sedentary adults with T2D (n=130) in 2 primary care clinic sites to test two aims.

Aim 1: Determine the effectiveness of a 12 week evidence-based physical activity program delivered by designated clinical staff and physician assistants, as compared to usual care, on:

1a) physical activity by accelerometer (primary outcome) and physical activity predictor outcomes from the social cognitive theory (SCT) of behavior – e.g., self-efficacy, social-environmental support

1b) physical function by physical performance measures (secondary outcome) and the physical function predictor of lower extremity strength

Hypothesis 1: Objective physical activity and physical function will increase more in the intervention vs. usual care study group.

Aim 2: Assess process measures among patients, clinical staff, clinical providers, and practice leadership to determine acceptability and time burden.

Hypothesis 2a: Over 80% of intervention patients would recommend the intervention to a friend.

Hypothesis 2b: Over 80% of clinical staff/providers would recommend continuing to offer the intervention.

Impact: By determining the effectiveness of this program and by filling my training gaps, this K23 proposal has great translational potential to improve the health of adults with T2D. It also prepares me to be a national leader in the implementation of evidence-based physical activity programs at other clinical sites.

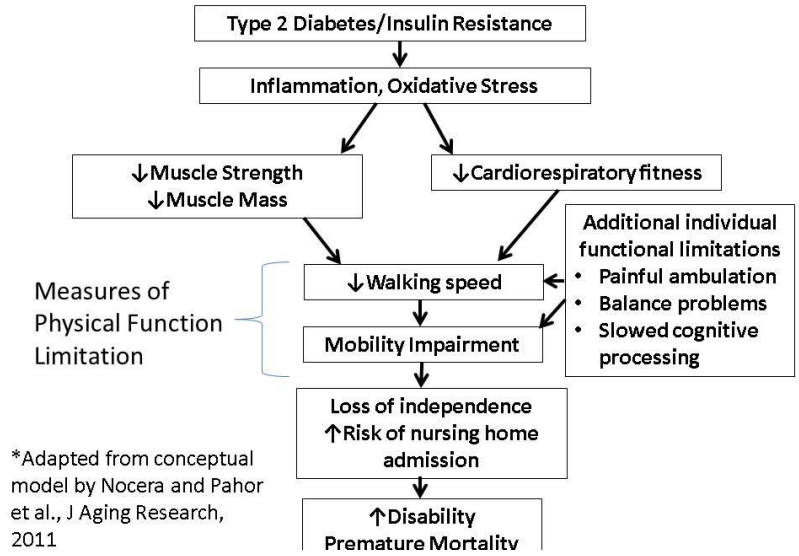
12. RESEARCH STRATEGY

Abbreviations: Type 2 Diabetes (T2D); Physical function limitations (PFLs); Patient-centered Medical Home (PCMH); Social Cognitive Theory (SCT)

12.1 SIGNIFICANCE

12.1.1. *Ongoing* Importance of physical activity for CV disease prevention in T2D The prevalence of diabetes mellitus has more than tripled in the past 30 years, and currently affects 25.8 million Americans.[6] T2D accounts for >90% of prevalent diabetes cases in adults.[7] Because people with T2D are at very high risk for CV disease, people with T2D are a high priority NHLBI study population.[8-11] Several large observational studies support regular physical activity as a potent therapy to reduce CV mortality in people with T2D.[12-15] A recent meta-analysis of prospective cohort studies found improved CV outcomes in participants with diabetes by physical activity strata (HR = 0.61 (0.47-0.80) for CV mortality for highest vs. lowest physical activity levels).[16] Data from RCTs have been mixed, as lower stroke event rates (HR = 0.62 (0.35-0.98) were observed in the intervention vs. placebo group of an RCT of a behavioral intervention that increased physical activity[17], but the Look AHEAD study was stopped for lack of group differences in CV outcomes[18]. Lower than expected CV outcomes in both Look AHEAD study groups may have under-powered this study to detect an intervention effect.[18] Overall, the consistent benefits of regular physical activity with regard to cardiorespiratory fitness, CV mortality, and all-cause mortality that have been observed in large cohort studies provide a convincing evidence base that regular physical activity improves CV health. Also, one study found mean annual health costs were ~$2000 less in people with T2D who performed physical activity ≥2 times/week vs. <1 time/week.[19] Thus, regular physical activity, a critical cornerstone of T2D treatment, may actually generate cost savings.[20]

Figure 2. Pathophysiology* of Physical Function Abnormalities in T2D



12.1.2. Why improve function? PFLs predict disability, loss of independence, and premature mortality for adults.[21-23] Regular physical activity can preserve function and reduce these adverse outcomes.[24-27]

12.1.3 Why develop a treatment specifically for adults with T2D? Adults with T2D develop worse physical function at an earlier age than their nondiabetic peers,[22,28] and regular physical activity is one of the only effective interventions.[24-27,29] Adults with T2D may develop premature PFLs due to specific factors associated with T2D[8,22,30-40] (Figure 2). Physical activity programs for adults with T2D and PFLs need to assess participants' balance, cognition, and symptoms during ambulation in order to avoid enrolling participants who are unsafe to perform physical activity independently.[24,41] Because regular physical activity improves

Figure 3. Activities during in-person vs. phone visits during intervention

Phone intervention visits
Point of contact: Telephone call
Clinic involvement:
- Health promotion clinic staff:
  - Brief counseling
  - Tailored to unique individual barriers/benefits from baseline surveys
  - Recommend short bouts of activity on most days
  - On individual basis, gradually↑activity goals and strength exercise goals towards U.S. physical activity guidelines
  - If clinical concerns arise, can call clinic nurse or physician assistant
  - Schedules next intervention visit

In-person intervention visits
Point of contact: Visit in primary care clinic with physician assistant
Clinic involvement:
- Usual vital signs and check-in
- Physician assistant:
  - Monitors intervention safety
  - Ensures proper form for strength exercises
  - Telephone handoff to health promotion clinic staff
- Health promotion clinic staff:
  - Phone counseling from off-site allows continuity of counselor throughout the intervention
  - Identical counseling content to phone intervention visit
  - Schedules next intervention visit

glycemic control,[42-44] treatment programs for adults with T2D should also monitor for glucose trends during the program and adjust medication doses as needed to avoid hypoglycemia. Existing physical activity programs have not always included these important safeguards — in part, because they were not integrated into clinics.[24] The proposed K23 trial will include these screening and treatment monitoring safeguards.

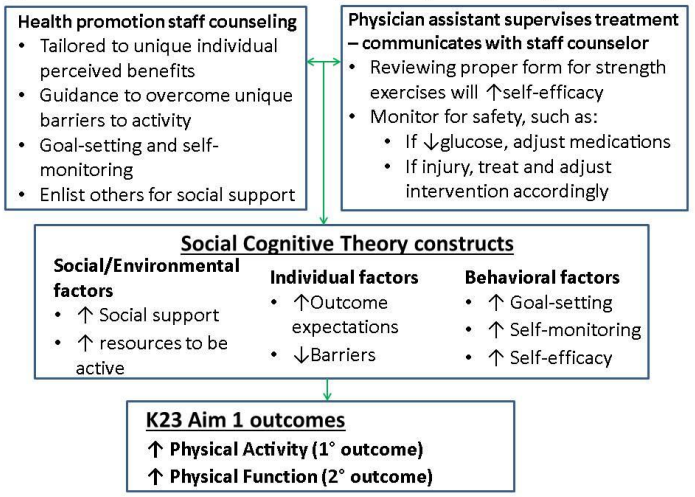
12.1.4 Why should we deliver an intervention in clinical practices? There are several reasons why clinical care settings are a highly relevant way to deliver interventions to treat adults with T2D and sedentary behavior. Clinical practices have key implementation features of **capability, motivation, and opportunity**.[45,46] Despite these features, primary care clinics do not deliver evidence-based counseling programs due to several concerns, such as: excessive staff and clinician burden, lack of reimbursement, and lack of training for clinicians/staff to deliver counseling.[47-49] To integrate an activity intervention in clinics, we need to develop programs that address these barriers in a way that may be replicated in other systems.

One way to address these barriers is developing at the national level. Primary care clinics have evolved dramatically over the past decade to better identify certain patient populations at high risk for disease — and proactively treat them. This model of care is termed the patient-centered medical home (PCMH), and its prevalence is growing rapidly.[50,51] An important PCMH characteristic is to use teams to manage patients' health. For example, PCMHs employ special health promotion clinic staff who call patients to address specific health targets (e.g., schedule routine diabetes visits, provide simple lifestyle counseling).[52-54] Using teams offers lower cost alternatives to treat sedentary adults with T2D: it costs less for health promotion clinic staff to deliver counseling compared to clinicians; also, clinicians can remain engaged to see patients in clinic to monitor treatment — a unique **capability** that we leverage in the proposed K23 (Figure 3). If effective, this K23 treatment model could be implemented in other PCMH clinics nationally. Clinics that are not PCMHs could also feasibly adapt this model and designate a clinician to deliver the counseling — but greater costs to the clinic and excessive clinician burden make the proposed K23 approach more optimal. The **motivation** for clinic leadership to deliver interventions is to improve quality of life and preserve functional independence for patients. The **opportunity** is to deliver a relatively simple yet impactful intervention in a way that provides repeated counseling to patients — regular and repeated counseling is important to change behavior.[55-59] Another opportunity is to deliver this treatment in a way that overcomes a translational barrier — reimbursement for in-person visits. Payers will likely be interested in this type of program due to the potential to prevent costly falls in adults with T2D and PFLs.[29]

12.1.5 Adapting effective physical activity interventions for populations with T2D

Social Cognitive Theory (SCT) has guided the behavioral interventions of many prior RCTs that improved physical activity behavior, including the VA Learning to Improve Function for Elders (VA LIFE) trial and the tailored counseling methods of DiLoreto et al.[24] The proposed K23 intervention includes SCT-informed tailoring to overcome physical activity barriers and promote facilitators instead of a prescriptive "one-size fits all" approach (Figure 4).[60] SCT considers behavior as an interplay between social/environmental factors, individual cognitive factors, and behavioral training (Figure 4).[61,62] With regard to increasing physical activity in adults with T2D, the role of tailoring to promote activity facilitators or "outcome expectations" is particularly important to address barriers such as **fear of injury and perceived difficulty with exertion**.[63,64] We also need to address potential T2D-specific facilitators such as motivation to reduce medication dosage and to prevent diabetic complications.[65-67] The Aim 1 pre-implementation phase will engage an expert advisory panel to adapt the K23 intervention to include tailoring to these and other T2D-specific barriers and facilitators — while ensuring the intervention remains simple enough for health promotion clinic staff to use.

Figure 4. Relationship of Intervention, Social Cognitive Theory, and Outcomes



11.1.7 Summary of Significance: One important way to reduce the burden of CV morbidity and *premature* mortality in people with T2D is to increase physical activity. Evidence-based behavioral interventions have increased physical activity[2,17] *and have also improved*

cardiorespiratory fitness[2] and stroke outcomes[17] in RCTs of people with T2D. However, in order to widely translate physical activity interventions for people with T2D, interventions need to be more affordable, less resource-intensive, and more integrated with clinical care than *the behavioral interventions tested in RCTs to date.[3,4] We propose an important next step to allow integration of behavioral interventions into clinical care - to develop simple, valid methods to systematically identify and assess participants' barriers and facilitators*.

My K23 research objective is to determine the feasibility and effectiveness of a Social Cognitive Theory-based behavioral counseling intervention (Aims 1-2) integrated into the primary care setting. The proposed research is significant because it *develops an intervention that is evidence-based yet brief enough to be implemented in clinical practice* for a population with disproportionate CV risk (T2D). The proposed work also addresses NHLBI Challenge 3.1 by identifying motivational factors related to physical activity – a priority behavioral risk factor for CV disease – in order to inform intervention strategies.

12.2 INNOVATION

I recently received Hartford Foundation funding to adapt the VA LIFE intervention[24] and pilot-test having health promotion clinic staff deliver it to older adults with PFLs — the CU LIFE pilot trial. The CU LIFE pilot provides an infrastructure that we propose to expand in the K23 to fully integrate an evidence-based physical activity intervention into primary care. The chief K23 **innovations/advantages** are detailed in ***bold italics*** (Table 4).

Table 4. Innovation of proposed Huebschmann K23

	VA Learning to Improve Function for Elders (VA LIFE)	Funded CU LIFE pilot trial (PI – Huebschmann)	Huebschmann K23 proposal
Study population	Sedentary adults 70-92 years (n = 398, 34% with diabetes)	Sedentary adults 65-85 years, with or without T2D; and with PFL of slow walk speed (Enrolled n = 2 in first month, none with T2D; proposed n=25)	Sedentary adults 50-85 years with T2D (n = 130 proposed to enroll)
Innovation from prior work	Delivered behavioral counseling by phone: 1) Effectively increased physical activity and improved function; 2) Less burden for participants than attending supervised exercise programs **Exclusion Criteria screening:** Research staff screen patients for eligibility **Counseling delivered by:** Research staff with behavior counseling training	Integrate phone counseling intervention into clinics: 1) adapted VA LIFE intervention for delivery by health promotion clinic staff; 2) With physical therapy mentor input, added exercises that resist body weight to improve strength more so than Theraband© exercises used in VA LIFE **Exclusion Criteria screening:** Research staff screen patients with PFLs for eligibility **Counseling delivered by:** Health promotion clinic staff who received training to deliver a brief, tailored intervention to adults with PFL	***1) Integrate screening into clinics*** ***2) In-person treatment visit enhances safety and provides reimbursement potential*** ***3) Robust mechanistic effectiveness assessment (Aim 1)*** ***4) Optimize CU LIFE counseling to address individual barriers and facilitators specific to T2D*** **Exclusion Criteria screening:** Clinic physician assistant assesses for K23 eligibility during special "Stay Strong" clinic visit for sedentary adults with T2D **Counseling delivered by:** Health promotion clinic staff who will receive training to deliver a brief, tailored intervention to sedentary adults with T2D
Next steps		Huebschmann K23 proposal	Future R01 – see section 12.3m.

12.3 APPROACH

12.3a. OVERALL RCT STUDY DESIGN The overarching goal of this proposed research is to determine whether an evidence-based intervention that is reimbursable in U.S. clinics will improve physical activity and physical function. To our knowledge, no studies have fully integrated these research programs into clinical practice. Thus, we designed this study to determine the effectiveness (Aim 1) and acceptability/time burden (Aim 2) of integrating an intervention for adults with T2D. For Aims 1-2, we will assess outcome measures at time = 0 (baseline) and time = 3 months (post-intervention). We provide a detailed timeline for our proposed research procedures (Table 5) to complement the timeline of training and career development activities in section 4. (Career Development Plan)

Table 5. K23 project timeline												
Year												
Quarter												
	Year 1 – 2015				Year 2 – 2016				Year 3 – 2017			
Quarter	1	2	3	4	1	2	3	4	1	2	3	4
Project Phase												
Adaptation of screening and intervention for primary care	x	x										
Pilot-test intervention		x										
Patient recruitment and Screening		x	x	x	x	x	x	x	x	x		
Randomization of patients to intervention or usual care with accumulated participant goal (n) per quarter		5	20	35	50	65	80	100	115	130		
Data analyses of primary and secondary outcomes (Aim 1)											x	x
Process measure evaluation in participants and clinic system (Aim 2)			x	x	x	x	x	x	x	x	x	
K23 milestones: future grant submissions and manuscripts. See Table 3 timeline in "Career Development plan"		A			B		R01			R01		C

12.3b. ADAPTATION OF THE SCREENING ALGORITHM AND INTERVENTION FOR PRIMARY CARE

Table 6: Proposed K23 Exclusion criteria for Screening Visit - to be optimized in pre-RCT Adaptation phase
Dementia (Folstein Mini-Mental Status Exam < 24)[24] or clinical diagnosis
Excessive fall risk: Cannot hold semi-tandem stance for ≥10 seconds [68]
T2D-related safety concerns: Prior diabetic foot ulcer; Charcot foot; asymptomatic hypoglycemia[20]
Severe uncontrolled hypertension (BP >180/100)[24]
Excessive hearing or visual impairment for counseling[24]
Limited life expectancy: active treatment for malignancy[24]
Performs regular physical activity ≥20 minutes on ≥3 days/week, as per valid screening question from Activity Counseling Trial[55]: "Do you regularly participate in any physical activity such as walking, running, aerobic dance, swimming, or sports at least 3 times per week for 20 minutes or longer each time?".
Conditions that may limit response to intervention: chronic liver disease (transaminases >2 times normal limits), chronic kidney disease (serum creatinine >1.5 mg/dl or urine microalbumin >30 mg/g), anemia (Hb < 11 mg/dl), or pregnancy

Because we are adapting the pilot CU LIFE intervention that is currently coordinated by research staff, we will need a pre-RCT adaptation phase to fully integrate the study procedures into the clinic. In this adaptation phase, the PI will meet monthly with an expert advisory team representing K23 mentors in physical activity in T2D (Dr. Regensteiner), endocrinology (Dr. Reusch), physical therapy (Dr. Stevens-Lapsley), physical activity behavior counseling (Dr. Dunn), health promotion clinic staff who will deliver the counseling, and clinic physician assistants who will conduct the screening and monitor the treatment.

Clinical screening algorithm (Table 6): First, we will optimize the clinical screening algorithm in consultation with our expert advisory team. Next, in months 4-6, the PI will train four clinic physician assistants (n = 2 from each clinic) to conduct the screening. The PI will field test the optimized screening algorithm until we achieve an outstanding κ inter-rater reliability ≥0.81.[69]

Tailor counseling to T2D needs: In months 0-3 of the pre-RCT Adaptation phase, we will also optimize the evidence-based clinical counseling program used in clinical practices by Di Loreto et al (Table 7).[70] One area of optimization will be to increase participant self-monitoring and accountability through the use of wearable activity monitors that provide feedback to participants on how well they are meeting their goals. Another area of optimization is to add diabetes-specific motivational factors to the counseling, such as fear of foot ulcers/hypoglycemia (barrier). In months 4-5, the PI will pilot-test the intervention with participants to obtain participant feedback on optimal methods of presenting the intervention content, such as formatting of materials that describe potential motivators, barriers, and physical activity programs (Table 7). In month 6, Dr. Dunn will aid the PI to train health promotion clinic staff to deliver the intervention in month 6 (Phase 2b). Training will include:

Table 7: Proposed K23 Intervention Counseling content - to be optimized in pre-RCT Adaptation phase
Motivation: Review health benefits of regular activity for people with diabetes – tailored to emphasize benefits of greatest interest to individual
Self-efficacy: collaborate with each participant to identify activity program that participant can confidently perform - advance weekly goals realistically by 2-10 min/week
Pleasure: Ask about prior exercise experiences to rule out boring/painful activities. Suggest several indoor and outdoor aerobic activities –participant selects ≥2 enjoyable activities
Support: Suggest walking or other activity with family/friends. *K23 Optimization:* Wear FitBit© throughout the 12-week intervention to provide motivational reminders
Identify personal pros/cons of change: Probe understanding of value of making this change. Assess uncertainty about committing to this change and perceived barriers to activity. *K23 Optimization:* After open-ended questions, inquire about T2DM-specific barriers of painful activity, fear of injury, and fear of hypoglycemia
Overcome barriers: Rather than suggesting solutions, counselor invites participant to solve the barriers to activity he/she identified. Counselor adds advice on time management strategies.
Tracking: Participant records daily type and times of activity *K23 Optimization:* Wearable device simplifies ability to track activity

- how to use brief motivational interviewing techniques to increase physical activity behavior[71]
- how to tailor intervention content to the participant's stage of change[72] (e.g., contemplation, action)
- how to tailor intervention to unique individual barriers/benefits of physical activity

12.3c. RECRUITMENT

For the past 5 years, the University of Colorado has used designated health promotion clinic staff to meet the prevention-focused needs of its primary care clinics (see description of PCMH in Significance). These staff receive monthly customized reports of primary care patients who warrant outreach. These reports are generated automatically from the electronic health record by a computer program.

As of May 5, 2014, there are currently **1400 patients** in our two University of Colorado Internal Medicine clinics who may qualify for the proposed study based on a T2D diagnosis and age of 50-85 years — population estimates suggest ~60% of these patients will be sedentary.[58,73] On a monthly basis during the K23, the health promotion clinic staff will receive a list of clinic patients who meet inclusion criteria that is pulled from the electronic health record by an electronic query: adults aged 50-85 years with ICD-9 diagnosis code for T2D.

The health promotion clinic staff will call interested and eligible adults from the list to offer a special type of primary care clinic visit: "Stay Strong: Learning to Improve Physical Function and Prevent Falls ("Stay Strong" visit). The purposes of the "Stay Strong" visit are: 1) to provide standard-of-care fall prevention information to all sedentary adults with T2D; 2) to screen for K23 eligibility. This approach is consistent with the PCMH focus to proactively target the health needs of specific patient subpopulations.[74]

12.3d. SCREENING

During the "Stay Strong" clinic visit – a trained physician assistant reviews fall prevention and community physical activity options, and uses the optimized screening algorithm (Table 6) to assess exclusion criteria. Our clinics will bill insurance for this clinic visit and for the other in-person clinic visits (Visits 4, 6, and 8) for the services provided by the physician assistant. We will not bill insurance for the phone counseling services provided in visits 4-9; the costs for the staff time needed to provide phone counseling are covered by the grant.

12.3e. ENROLLMENT

Study Population: Patients who are interested in participation and meet inclusion criteria (T2D, age 50-85 years) and do not meet exclusion criteria (Table 6) will attend an enrollment visit (Visit 1, V1). After informed

consent, participants will undergo 1:1 patient-level randomization to the intervention or usual care group. (Figure 5)

Study Settings: Enrollment (V1), Baseline testing (V2-3), and Exit testing (V10-11) will be conducted in the CCTSI outpatient Clinical Translational Research Center.

12.3f. INTERVENTION GROUP

Figure 5. Huebschmann NIDDK K23 Study Flow

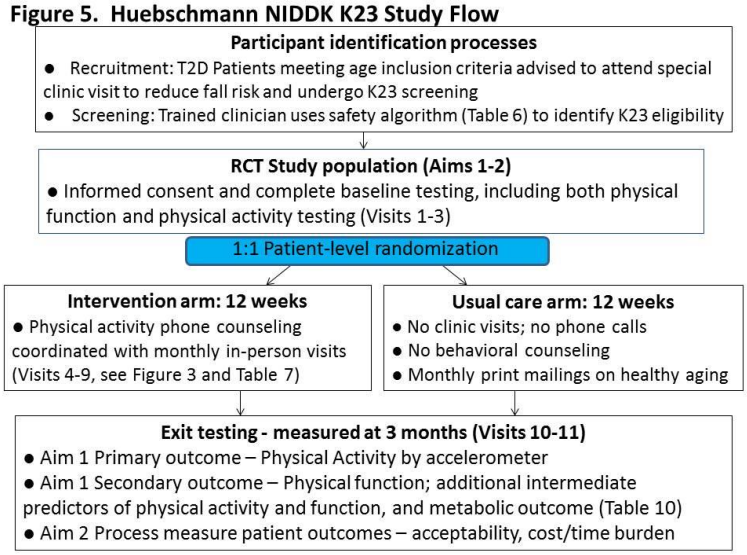


Table 8 Study visit activities, by study group

Visit	Phase	Intervention	Usual Care
1	Enrollment	Consent, baseline testing	Same as intervention arm
2-3	Baseline time (t) = 0 weeks	Baseline covariate and outcome testing	Same as intervention arm
4	t = 2 weeks	In-person clinic visit * with phone counseling†	None
5	t = 4 weeks	Phone counseling†	Print mailing on aging topic
6	t = 6 weeks	In-person clinic visit * with phone counseling†	None
7	t = 8 weeks	Phone counseling†	Print mailing on aging topic
8	t = 10 weeks	In-person clinic visit * with phone counseling†	None
9	t = 12 weeks	Phone counseling†	Print mailing on aging topic
10-11	Exit testing, t = 3 months	Exit covariate and outcome testing	Same as intervention arm

*Clinic visit is to teach and monitor form for strength exercises, to assess for safety concerns during treatment, and to coordinate with health promotion clinic staff counselor (see Figure 3 in Significance)
†Phone counseling delivered by health promotion clinic staff

The proposed intervention is based on SCT (Figure 4 in "Significance") and seeks to increase physical activity and improve strength by addressing individual, behavioral, and social/environmental factors. The health promotion clinic staff will deliver counseling by phone on a bi-weekly basis — a clinic physician assistant will coordinate with the counselor during in-person clinic visits (Figure 3 and Table 8), teach participants to perform strengthening exercises; and assess for safety concerns, such as hypoglycemia. We optimized the existing VA LIFE intervention in our funded CU LIFE pilot, by simplifying the VA LIFE counseling guide for delivery as brief, tailored counseling by health promotion clinic staff (see Appendix), and by adding strengthening exercises that engage multiple muscles (see Appendix). To ensure the intervention is brief enough for clinical use and to incorporate T2D-specific barriers and facilitators, we will make further adaptations in the pre-RCT Adaptation phase, as described above in 12.3b.

In addition to behavioral counseling targeting SCT constructs (Figure 4 in Significance), counselors will assist participants in the intervention group to set specific goals for physical activity in a paper log and on an electronic FitBit activity tracking device (see Appendix). Participants will record their actual physical activity next to their goals for easy review during counseling visits. Health promotion clinic staff will encourage participants to advance goals towards meeting U.S. physical activity guidelines of 150 minutes/week of moderate intensity activity (e.g., brisk walking) and 2-3 days/week of strength activities consisting of cycles of 5-10 repetitions of sit-to-stand, toe stand, chair dip, and side step-down (see Appendix).[75] Although achieving guidelines is a long-term physical activity goal, counselors will help patients to work towards this goal systematically but gradually. Participants and counselors will determine each person's rate of physical activity increase to accommodate unique factors associated with their T2D, functional limitations, and fitness.

12.3g. USUAL CARE GROUP

Participants in the usual care arm will receive three mailings during the intervention phase (Table 7). Health promotion clinic staff will mail materials from the Center for Disease Control and Prevention website that address general healthy aging topics: i.e., advanced directive care planning, vision and hearing changes with aging, respectively. These mailings will be the only research contacts with participants during the 12-week intervention phase.

12.3h. PRELIMINARY DATA PERTINENT TO THE APPLICATION

I and other study team members have collected study data in primary care clinical settings and clinical trial settings that demonstrate the feasibility of collecting the proposed measures. In addition, these data suggest that the proposed screening and behavioral intervention can be implemented in primary care systems that use health promotion clinic staff. Finally, these data suggest that the proposed intervention will improve the proposed physical activity measures that are strongly linked to physical function.

Preliminary data – Behavioral counseling by health promotion clinic staff I led an RCT for patients with uncontrolled hypertension of an intervention that included health promotion clinic staff counseling. Health promotion clinic staff called intervention patients and delivered brief, tailored counseling about lifestyle measures to control blood pressure, and arranged a primary care clinic visit.[54] We did not contact usual care patients. Because this intervention improved process outcomes related to blood pressure control and had high acceptability to patients and clinicians,[54] our clinics have continued this hypertension management process.

Table 9 Population Characteristics for Preliminary Data on Correlations between Physical Function and Physical Activity

	Overweight, sedentary adults (n = 12)
T2D (%)	58
Age (years, mean (SD))	61.1 (5.4)
BMI (kg/m^2, mean (SD))	30.2 (2.6)
Accelerometer-measured Physical activity (Combined moderate-vigorous intensity minutes/week, mean (SD))	91.0 (97.3)
Cardiorespiratory fitness (maximal oxygen uptake, ml/kg/min)	21.9 (1.5)
Physical function: Rapid, timed 400-meter walk, seconds (mean, SD)	300.4 (56.7)

Preliminary data -Physical activity and physical function outcome measures I have preliminary unpublished data on physical activity, physical fitness and physical function performance data in an ongoing study of sedentary, overweight older adults aged 50-70 years with and without T2D (Table 9). We measured physical activity and function by methods proposed in this application — accelerometer and the time needed to complete a 400-meter walk at the most rapid pace possible. As others have published,[20,24,26,56-58,76] we also found strong correlations between higher levels of physical activity measured by accelerometer (K23 1° outcome) and better physical function, as measured by a shorter time required to complete a rapid 400-meter walk (r = -0.52). These data support the conceptual framework of this study (Figure 2) by demonstrating the relationship between the outcomes of physical activity and function.

Preliminary data on 4-week phone-based activity counseling tailored to Dishman barriers surveys responses
Separate from our preliminary data in Tables 8-9, we have pilot-tested the delivery of tailored telephone-based counseling to 3 older adults with T2D (aged 67.3 ± 7.5 years, mean ± SD). Over 4 telephone-based counseling visits tailored to each participant's physical activity barriers responses,[77] we demonstrated an increase in combined moderate-vigorous physical activity levels by 142 minutes/week across 3 participants (from 65 ± 80 to 207 ± 87 minutes/week, mean ± SD).

Preliminary data on improved activity and function in response to interventions
Study team mentors (Judith Regensteiner, PhD. Andrea Dunn, PhD) have been active investigators in several, large behavioral physical activity interventions in clinical trials, primary care, and community settings that demonstrated improvements in outcomes of physical activity and physical function.[55-59] These trials have all used common behavioral tools of regular, repeated staff contact with participants to set goals, track activity, and overcome barriers to activity. Some of these trials included older participants with some physical functional impairments similar to those found in the participants we propose to enroll, although our trial will be substantively different by its use of clinical staff: 1) to identify patients who might safely participate; 2) to deliver such interventions.

Summary: Taken together the preliminary data collected support the idea that an intervention in a clinical setting which allows for screening to identify appropriate patients and then implementing a clinic based intervention has the potential to improve physical activity and function in sedentary adults with T2D.

12.3i. OUTCOME MEASURES (see Table 10 on next page)

12.3j. POWER CALCULATION AND DATA ANALYSES FOR AIM 1 (EFFECTIVENESS)

Power Calculation: We used PASS version 11 to calculate power for the physical activity outcome.[78] Aim 1 was powered based on a previously observed effect size of Cohen's d = .61 when comparing a physical activity intervention to an education control group on physical activity of moderate-to-vigorous intensity[79] among older, obese adults. Assuming similar sized effects in the current study and a two-sided alpha of 0.05, the proposed sample size of n=90 will provide over 80% power to detect differences between the activity intervention and usual care for Hypothesis 1. If our effects match that of our preliminary data (increase in combined moderate-vigorous physical activity levels by 142 minutes/week across 3 participants (from 65 ± 80 to 207 ± 87 minutes/week, mean ± SD), then we will have over 95% power to detect differences between the activity intervention and usual care. Enrollment of n=130 was planned to allow for up to 30% attrition. For Aim 1b, the proposed sample size will be sufficient to obtain stable means and standard deviations in order to calculate an accurate effect size estimate for physical function outcomes.

Data analysis: Before conducting the analyses by aim, we will assess descriptively and graphically the mean and distribution of each study outcome and covariate, in order to assess for outliers and skewed distributions. If variables are not normally distributed, we will consider logarithmic transformation.

Aim 1 Data Analysis

Hypothesis 1. Using intent to treat principles, we will test for differences between the intervention and usual care groups on physical activity at the 3 month assessment. We will assess the intervention effect size of change in physical activity from baseline testing to 3 months using an ANCOVA model with adjustment for age; covariates from Table 10 (e.g., cognitive processing speed); and each participant's baseline score. Adjustment for baseline score is useful in this relatively small RCT to eliminate any potential baseline differences between groups that may occur despite the randomization procedure. We expect that the mean physical activity at 3 months will be significantly higher in the intervention group than in the usual care control group. Every attempt will be made to ensure high retention rates at posttest, although some attrition is to be expected. The level and patterns of missing data will be evaluated relative to intervention condition and other baseline characteristics to determine whether there is systematic bias in the missing data. If necessary and appropriate, based on the level and patterns of missing data, state-of-the-art techniques (e.g., multiple imputation) will be used.

Aim 1 secondary outcomes. The analyses for Aim 1 secondary outcomes will be used to detect trends and to provide necessary data to calculate the sample size needed to detect differences in a larger RCT. We will assess the intervention effect size by calculating a Cohen's d effect size comparing the means of the two groups at the three-month follow-up. We will use separate ANCOVA models to assess pre-post intervention changes in the following outcomes listed in Table 10: physical function by 400-meter rapid gait speed (differentiates adults with higher baseline function); Short Physical Performance Battery (differentiates adults with lower baseline function); intermediate physical activity behavioral constructs from SCT; intermediate functional outcome (lower extremity strength); and metabolic outcome (Hemoglobin A1c).

Table 10. Outcome, Predictor, and Covariate Measures for Huebschmann K23			
Outcome	**Instrument**	**Variable**	**Measure**
Physical Activity outcomes			
Objective physical activity	Actigraph GT3x+ accelerometer measures physical activity objectively as minutes/week of moderate intensity and vigorous intensity physical activity, respectively.[80] We define moderate intensity levels by the methods of Freedson et al.[81] Participants will wear the Actigraph for a 7-day period pre/post intervention. We will ensure measurement during a typical 7-day period and will use standard wear-time validation procedures to ensure valid weekday and weekend data. Actigraph data will be collected on the 7 days between physical function and VO_2max testing.	Continuous	Aim 1 1° outcome
Physical activity behavioral constructs from SCT	Standard survey measures to assess the following physical activity behavior assessments of constructs from SCT: **Self-efficacy** to do physical activity of increasing duration;[82,83] **Social-environmental support** is a valid measure of how others support one's healthy lifestyle choices;[84] Lower barrier scores on the **Dishman physical activity barriers survey** are associated with higher levels of physical activity;[77] **Physical Activity outcome expectancy for elders survey** includes positive elements of physical activity for older adults, including health-related factors – better scores are associated with higher physical activity levels[85]	Continuous	Aim 1 Predictor variable: physical activity (PA predictor)
Physical Function outcomes	All physical function outcomes will be measured after a 4-hour fast and under the same conditions pre/post intervention.		
Cardiorespiratory fitness (VO_2max)	To assess cardiorespiratory fitness, we measure breath-by-breath utilization of oxygen (VO_2) and carbon dioxide (VCO_2) with a Medgraphics Ultima CPX metabolic cart (Minneapolis, MN). We also measure blood pressure (auscultation), and cardiac status (12-lead ECG). To determine VO_2max, subjects perform treadmill exercise to exhaustion using a standard protocol.[86,87] We define VO_2max per standard practice.[86]		
Physical function	400-meter rapid gait speed test measures fitness and mobility; it is **sensitive to change for adults with minimal to mild functional impairment**; predicts disability and mortality.[88] Physical function measures will be assessed on a separate study date from the VO_2max testing.	Continuous	Aim 1 2°outcome
Physical function	The Short Physical Performance Battery (SPPB) measures function with the following valid subscales: balance, usual walking speed, and repeated chair rise. The SPPB is **sensitive to change for adults with moderate to severe functional impairment**, and predicts disability and mortality.[68,89]	Ordinal, range 0-12	Aim 1 2°outcome
Lower extremity strength	Lower extremity strength will be measured as leg extensor (quadriceps) and leg flexor (hamstring) strength using Dr. Stevens-Lapsley's laboratory's established techniques.[38,90]	Continuous	Aim 1 Function predictor
Grip strength	Hand grip strength will be measured by dynamometer.[91]	Continuous	Aim 1 2°outcome
Metabolic control outcome			
Hemoglobin A1c	Average glycemic control measured by standard methods[92]	Continuous	Aim 1
Covariates for adjustment			
Depression symptoms	Center for Epidemiologic Studies Depression Scale measures depressive affect severity and is valid in people with[93,94] and without T2D.[95,96]	Continuous	Aim 1 covariate for adjustment
Lower extremity arthritis pain symptoms	Western Ontario and McMaster Universities Arthritis Index– valid measure of knee and hip pain and stiffness.[97]	Continuous	Aim 1 covariate
Cognitive processing speed	Stroop test –measures cognitive processing speed as a valid predictor of cognitive function in adults with and without T2D.[98-100]	Continuous	Aim 1 covariate

DEXA scan	DEXA will allow the calculation of body composition as fat-free mass and total mass so that we may report exercise performance levels standardized to these body composition measures.	Continuous	VO_2max covariate for adjustment
Cognitive executive function	Behavioral Dyscontrol Scale – valid measure of executive function in adults with and without T2D.[101,102]	Continuous	Aim 1 covariate
Process outcomes			
Acceptability	Percent of intervention patients who would recommend intervention[103]; Percent of clinical providers/staff who recommend continuing to offer the intervention to patients[103]	Percentile	Aim 2
Time burden	Patient time required for each intervention visit[103]; Staff/provider time required for each intervention visit[103]	Continuous	Aim 2
Safety outcomes	Participant report of outcomes after baseline testing: falls, musculoskeletal injuries, foot ulcers, hypoglycemia[20,24,57]	Continuous	Safety

12.3k. ANALYSIS OF ACCEPTABILITY OUTCOMES (Aim 2 and Safety analysis)

Aim 2 Statistical analysis: We will use surveys to descriptively assess the pilot RCT outcome of intervention acceptability. **Acceptability levels ≥ 80% for patients (Hypothesis 2a) and for clinic providers (Hypothesis 2b) will support the intervention as acceptable.**[103] Because acceptability may vary by clinic staff/provider type due to differing intervention burden/benefits by role, we will assess acceptability levels separately among different types of clinic staff/providers (i.e., medical assistants, primary care providers, chronic disease management counselors, physician assistant counselors, clinic leaders).[103]

Aim 2 Descriptive analysis of time burden: For each treatment visit, health promotion clinic staff will document the time required to complete the intervention for patients, clinic providers (in-person treatment visits), and clinic staff (telephone counseling). If the intervention is effective, these time burden estimates could be used to generate future cost analyses.

Safety analysis: For ethical reasons, in addition to the acceptability outcomes addressed in Aim 2, we will monitor for study group differences in safety-related outcomes, in order to assess for any potential study harm. We selected the following safety outcomes based on relevant use in prior trials and per expert description of safety concerns in T2D; falls, musculoskeletal injuries, severe hypoglycemia (glucose <60 mg/dl or hospitalization/Emergency department visit for hypoglycemia.[20,24,57] At study exit visit 9, we will ask participants if any of the following safety-related outcomes occurred since baseline testing was completed in visit 2: fall requiring clinical evaluation; fall that did not require clinical evaluation; musculoskeletal injury requiring clinical evaluation; musculoskeletal injury that did not require clinical evaluation; severe hypoglycemia (glucose <60 mg/dl or clinical evaluation for hypoglycemia), foot ulceration. For each safety outcome measured, we will descriptively report these as both dichotomous outcomes (Yes/No) as well as the frequency of safety events (e.g., number of hypoglycemic episodes). We will use ANCOVA to obtain preliminary data on the group differences in safety outcomes with adjustment for baseline conditions that may increase safety risk. Baseline conditions that may increase safety risk include the following: baseline moderate-to-severe impairment on SPPB (baseline score <10), prior history of fall, slowed cognitive processing speed).

12.3l POTENTIAL PROBLEMS AND ALTERNATIVE STRATEGIES We have planned alternatives for potential problems that may arise. For example, if participants report new medical concerns or symptoms during the telephone counseling sessions with the health promotion clinical staff, staff members will transfer the patient to the clinic triage nurse to evaluate the patient's symptoms. Also, if participants report new musculoskeletal pains to the health promotion clinic staff, the staff member will send an electronic health record note to the physician assistant conducting the in-person treatment visits to advise the patient on any recommended treatment or activity restrictions.

12.3m EXPECTED OUTCOMES/FUTURE DIRECTIONS As adults with T2D age, they develop PFLs at an earlier age than their nondiabetic peers — in part due to the sedentary behavior associated with T2D. PFLs in older adults increases risk for institutionalization, mortality, and poorer quality of life so that people with T2D are particularly at risk. The proposed goal is to improve the physical function mediator of physical activity in older adults with T2D and sedentary behavior in primary care settings. Our rationale is that behavioral theory-

informed interventions increase physical activity and function. What patients need is the translation of these interventions to settings with the greatest reach and impact — in clinical practice. We will integrate a behavioral intervention into primary care clinics to treat sedentary adults with T2D. If the K23 preliminary data suggest that the intervention will improve physical function, the resultant R01 will be powered to detect improvements in physical function and to assess intervention costs and other outcomes relevant to future implementation. Even if the K23 intervention does not improve physical function, we will observe individual changes in physical function that will vary by factors such as baseline levels of predictors of activity and function or covariates (Table 10). In this case, the future R01 would assess the mechanisms of change in physical function in sedentary adults with T2D and would more precisely estimate subpopulations that are more likely to respond to an intervention. For example, if K23 participants with higher baseline muscle strength were more likely to improve their 400-meter walk function outcomes than participants with lower muscle strength, the R01 would assess the mechanisms of improvement in 400-meter walk with regard to baseline muscle strength and predictors of muscle strength such as insulin resistance and age,[33,104] and it would also assess the range of baseline muscle strength that predicts response to the intervention). In addition, we would optimize the K23 intervention to improve its effects on outcomes that did not respond; for example, if hamstring muscle strength improved but quadriceps muscle strength did not improve, we could alter our strengthening exercises recommendations to increase the number or frequency of quadriceps strengthening exercises.

This scientific proposal directly addresses a “key research objective” that was developed in the 2011 Federal Diabetes Mellitus Interagency Coordinating Committee’s strategic plan: “to determine optimal strategies to improve and sustain lifestyle strategies for older adults with diabetes”. By determining the effectiveness of this program and by filling my training gaps, this K23 proposal has great translational potential to improve the health of sedentary adults with T2D. It also prepares me to be a national leader in the implementation of evidence-based physical activity programs at other clinical sites.

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