# Study Protocol

Efficacy of a novel web-based physical activity intervention designed to promote adherence to physical activity guidelines in adults with obesity

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**EXTERNAL (NON-EMORY) COLLABORATORS**

Lora E. Burke, Professor, University of Pittsburgh, Department of Health and Community Systems (No IRB approval is being sought at Pitt).

Susan Sereika, Professor, University of Pittsburgh, Department of Health and Community Systems (No IRB approval is being sought at Pitt).

Britney Beatrice, Instructor, University of Pittsburgh, Department of Sports Medicine and Nutrition (No IRB approval is being sought at Pitt).

Bethany Gibbs, Associate Professor and Chair Department of Epidemiology and Biostatistics, West Virginia University School of Public Health (No IRB approval is being sought at WVU).

Kirk Erickson, Director of Translational Neuroscience, AdventHealth Research Institute (No IRB approval is being sought at AdventHealth).

David Ogutu, Founder and CEO, Ritiko LLC (No IRB approval is being sought at Ritiko).

La'vette Wagner, Health Coach LLC (No other IRB approval is being sought).

Redet Kebebe, Research Coordinator (No other IRB approval is being sought).

**PRINCIPAL INVESTIGATOR:**

Jacob Kariuki, PhD

Nell Hodgson Woodruff School of Nursing

Telephone Number: [redacted]

[redacted]

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**REVISION HISTORY**

| Revision # | Version Date | Summary of Changes |
|---|---|---|
| 1 | 2<br>3/7/2023 | We clarified in section 5 that the health coach will be a member of the study team. We also added Heather Milton as a member of our study team. |
| 2 | 3<br>3/16/2023 | In section 20, we have clarified that all the technologies to be used in this study, including Digital Ocean webhosting platform, PATH website, Twilio, SR Fax, Actigraph, Fitbit, and Withings apps were reviewed and approved by Emory University's Enterprise Information Security Team.Added details of external team members in section 27 |
| 3 | 4<br>8/25/2023 | In this modification, we update that we are moving our web-hosting platform to Amazon Web Services (AWS) at Emory, make changes in the study staff and external team members who will have access to the data, make minor modifications in the study protocol and short study title, change informed consent platform from DocuSign to REDCap, and add recruitment materials. |
| 4 | 5<br>10/12/2023 | In this modification, we add the documentation needed for us to recruit participants within Emory Health Care and via GCTSA social media sites. We also provide more details clarifying that both the intervention and control groups will be asked to take their blood pressure and step on the scales during their twice a month meeting with the study team. This information was already in the approved consent form. |
| 5 | 6<br>05/10/2024 | We have added two new end of study surveys (System Usability and Early Childhood Adversity) to help us evaluate the participants experience with PATH and life experiences that may impact study outcomes. The additional questionnaires would take about 15 mins. Also, the need to promptly evaluate adverse events has made it untenable to blind investigators. This mofication clarifies that only the staff conducting the assessments are blinded.<br><br>Lastly, we add a consent to give participants an option to continue using PATH without coaching at the end of study. |
| 6 | 7 | Add new study team members to meet emerging needs. |

| | | |
|---|---|---|
| | 12/16/2024 | |

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**PROTOCOL TITLE**: Efficacy of a novel web-based physical activity intervention designed to promote adherence to physical activity guidelines in adults with obesity

## 1. Study Summary

| | |
|---|---|
| **Project Title** | Efficacy of a novel web-based physical activity intervention designed to promote adherence to physical activity guidelines in adults with obesity |
| **Project Design** | Two arm, parallel randomized controlled trial |
| **Primary Objective** | Pilot test the efficacy of the PATH intervention for improving adherence to the PA Guidelines |
| **Secondary Objective(s)** | Compare the effects of the PATH intervention on CVD risk factors |
| **Research Intervention(s)/Interactions** | Our previously developed web-based Physical Activity for The Heart (PATH) intervention |
| **Study Population** | Adults with obesity |
| **Sample Size** | 88 |
| **Study Duration for individual participants** | 6 months |
| **Study Specific Abbreviations/ Definitions** | PATH: Physical Activity for The Heart<br>PA: Physical activity |
| **Funding Source (if any)** | National Heart Lung and Blood Institute |

## 2. Objectives

The United States' 2018 Physical Activity Guidelines recommend that American adults should achieve ≥150 min of moderate intensity PA, 75 min of vigorous PA, or an equivalent combination of both (MVPA) weekly.[1,2] Yet, adherence to these Guidelines is low, with 26% of adults with normal weight and 14% of adults with obesity attaining the minimum recommended PA levels.[1,3,4] The low PA levels are associated with the rising prevalence of obesity and increase the relative risk of stroke, coronary heart disease, and diabetes by 60%, 45%, and 30%, respectively.[5–7] Since individuals with obesity are more vulnerable to cardiovascular disease (CVD) and its risk factors, weight loss is recommended.[8] Yet, even without weight-loss, PA significantly reduces CVD risk.[1,9,10] However, individuals with obesity face complex multifaceted barriers that reduce their engagement in PA.[11,12]

Barriers to PA associated with obesity include stigma, shame, poor fitness, and low self-efficacy. These evoke fear of embarrassment and pain, contributing to aversion of PA.[12–14] To mitigate these barriers, web-based PA programs targeting adults with obesity have been developed. Preliminary data suggest improved retention, but the effects on PA are heterogeneous.[15] Limitations of these interventions include lack of human contact, 'one-size-fits-all' strategies, unmet weight-loss expectations, and generic content that fails to address the barriers

associated with obesity.[12,16] We[17] and others[11,12] have reported that individuals with obesity prefer programs that are convenient, fun to engage in, and feature people who they can relate to in body size, fitness level, and age. Yet, there is a paucity of PA interventions intentionally designed to flexibly incorporate these preferences.[12,18,19]

To address the limitations of previous interventions, our research team designed the web-based PA for The Heart (PATH) intervention (described in Preliminary Studies). PATH leverages openly accessible platforms, such as YouTube, to provide workout videos that match the specific preferences expressed in our formative studies and the extant literature. In developing PATH, we employed an iterative bottom-up approach where our target population was engaged in the selection and rating of the workout videos. Then, highly rated workouts (≥3.5/5 stars) were vetted by the study team for content relevance and safety, and then curated on our PATH website in 3 intensity levels (beginner, intermediate, proficient) to foster gradual progression from low to high intensity PA. We added backend features that enable a remote health coach to help users set their PA goals and select a PA regimen that is safe for their fitness level. Each PATH user has a personalized dashboard displaying their recommended workouts and progress towards their PA goals.

We have successfully beta tested the PATH platform (N=25) and have completed a 12-week feasibility study where we met our recruitment goal (N=82) and attained excellent retention (96%). Intervention engagement was high, and the PATH group increased objective MVPA by 59 min/wk vs. no change in control group, indicating preliminary efficacy. Recently, we submitted a R01 proposal to test the efficacy of PATH in promoting short- and long-term adherence to PA Guidelines in a diverse sample of inactive adults with obesity. **The proposal was ranked at 33$^{rd}$ percentile, with the study section recognizing the significance of using a highly scalable intervention to overcome PA barriers in obesity, and the innovativeness of the PATH Fresher algorithm that leverages users' feedback and the YouTube recommender system to identify workouts that cater to different audiences.** However, the reviewers noted that the significance is reduced by the "lack of compelling rationale for sole focus on PA without considering other obesity risk factors such as diet/weight reduction." They also observed weaknesses related to our exclusion criteria, and a control condition that was not well-matched to the treatment group. In this proposal, we plan to address the limitations identified by the reviewers as part of our resubmission/grant readiness strategy. We propose to pilot test the revised R01 protocol by conducting a two arm, 6-mo randomized controlled trial (RCT) of 88 insufficiently active adults with obesity who will be assigned to either the PATH intervention or an attention control group to address the following aims:

**Aim1:** Optimize the PATH website and enhance the effectiveness of the PATH Fresher algorithm in identifying workout videos that match specific user preferences. Effectiveness of the PATH Fresher algorithm will be indicated by its ability to analyze PATH users' data, spin up new browser sessions in the background to activate YouTube recommender system, and select workouts that are highly rated by target users (≥3.5/5 stars).

**Aim2**: Curate and pilot nutritional resources focusing on improving diet quality. The print-based resources will be curated from an extensive library of standard behavioral treatment content previously developed and validated

by Co-I Burke. The resources addressing diet quality components will be disseminated via email to all study participants monthly. The Healthy Eating Index will be used to assess diet quality at baseline and 6 mos.

**Aim3:** Evaluate the efficacy of PATH for improving adherence to the PA Guidelines. Outcomes: Objective MVPA via waist-worn Actigraph GT3X, step count via Fitbit, and adherence to the PA Guidelines at 6 mos.

*H: The PATH intervention group will have higher weekly MVPA and step count vs. the attention control group.*

**Aim 4:** To compare the effects of the PATH intervention on CVD risk factors. Outcomes: 10-year CVD risk score, Life's Essential 8™, weight, blood pressure, waist circumference, HbA1C, Adiponectin, lipids at 6 mos.

## 3. Background

During the 7th International Congress on Obesity in 1994, the famed nutritionist Dr. John Garrow contended that "the contribution of exercise to the treatment of obesity is trivial" because people with obesity are unable to do much exercise.[14] More than two decades later, the state of the science is unequivocal about the critical role of PA in mitigating CVD risk in obesity.[9] However, the full potential of PA in treating obesity has not been realized because 86% of adults with obesity do not adhere to the PA Guidelines.[4] In addition, adults with obesity are less likely to participate in PA programs, and when they do their non-adherence and dropout rates are high.[14]

The phenomenon of PA avoidance in obesity has been detailed in literature, but there is a dearth of programs that are designed to address the root causes.[12,14] In addition to common PA barriers,[20] individuals with obesity face weight-related impediments, including stigma, shame, poor body fitness, and low self-efficacy, which reduce their engagement in PA.[11,12,18] These impediments have been observed in white[11,12] and minority samples,[21–23] and inform ongoing efforts to develop web-based PA interventions that target adults with obesity. A recent review of web-based PA programs reported that only 3 of 13 studies focusing on adults with obesity attained significant improvements in PA.[18] Lack of human contact, 'one-size-fits-all' strategies or generic content, and unmet weight-loss expectations are thought to limit adherence and the utility of these interventions in adults with obesity.[12,14,16]



Fig 1. Screenshot of PATH user dashboard

Recent studies suggest that this clinical population prefers activities that are enjoyable, less exhausting, and doable in settings where they are not exposed to stigma or anti-obesity bias.[12–14] In *our prior work*[17] we have reported that many of our focus group participants preferred programs that focused on the health benefits of PA without emphasizing weight-loss, which although desirable can be fleeting/elusive.[24] Our investigative team also corroborated extant data[11,12,17,21,25]

suggesting interest in PA programs that provide vicarious experience[26] by featuring role models who are relatable in terms of body size, fitness level, and age. We[27] and others[28] have reported that vicarious experience is associated with improvements in exercise self-efficacy and PA. Yet, only a few PA interventions that target adults with obesity incorporate these preferred strategies in their programs. In response to the research gaps, we designed the PATH intervention, which incorporates the preferences expressed in literature and our formative research, guided by social cognitive theory (SCT).[26] PATH leverages YouTube,[29] to provide a variety of workout videos that feature PA models with diverse body sizes, fitness levels, and age (Fig 1). Since YouTube allows embedding of its videos on 3rd party sites for non-commercial use,[30] the vetted workouts are curated on the PATH website where they can be accessed without ads even at low internet speed (0.7 Mbps).[31]

Our feasibility data suggest that the PATH website includes content preferred by diverse participants, is very appealing, easy to navigate and promotes high intervention engagement. *The proposed research is significant because it will provide key evidence supporting the use of curated, openly sourced content to address PA barriers in obesity. Our novel intervention presents a resource-efficient strategy for designing behavior change programs and will inform future studies seeking to promote PA in other high-risk groups. If PATH improves adherence to the PA guidelines, it could provide a vital additional tool for mitigating CVD risk in obesity.* Adherence to the PA guidelines improves CVD risk, even when no weight-loss is attained.[10] The PATH intervention has a versatile translational potential as a stand-alone program to enhance PA or as a complement to a nutrition program seeking to promote weight-loss. The highly scalable program is accessible in any setting and can lessen the impact of unpredictable barriers to PA such as inclement weather or pandemics such as COVID-19.

**Innovation**

- We have leveraged open-source technology to create a PA program that provides a wide range of diverse, enjoyable workouts featuring PA models who look like the target population. The plan allows us to tap into the creativity of the global community of PA experts without engaging in the resource intensive process of creating new workouts. The pilot RCT participants rated the curated workouts as the favorite aspect of PATH.
- The innovative coaching platform on PATH website will facilitate a seamless collaboration between the coach and users in setting their PA goals and selecting the workouts to meet those goals. The set goal and selected workouts populate on user's dashboard and are updated on each coaching session. The active involvement of users in all aspects of PA prescription is a novel strategy for improving their long-term engagement in PA.
- PATH interfaces with many wearable sensors (e.g., Fitbit) and has a user-facing self-monitoring dashboard that displays progress towards the weekly PA goal and the recommended workouts to attain the goal. This innovative strategy motivates users to frequently log on the PATH website to track their progress in near real-time, and to conveniently access the workouts they selected, with the help of a coach, to attain PA goal.
- The moderated forum on the PATH website allows users to share and comment on each other's experiences, providing a sense of community and accountability while preserving the users' privacy. In our pilot RCT, the forum was used for encouragement and to share tips for succeeding in the program.
- The PATH website has a feedback loop, facilitated by intuitive tools embedded on each workout (comment box, 5-star favorability rating and rating of perceived exertion), that allows users to provide timely feedback on each workout they use. The feedback provides insights on issues to be addressed during the coaching

sessions. Aggregate feedback data are used to monitor overall sentiment and appeal of each workout.

- The PATH Fresher algorithm (on the website) analyzes PATH utilization metrics and interacts with the YouTube recommender system to identify new workouts that are comparable to those favorably rated by PATH users. The new recommendations are queued on the platform's back-end for vetting by study staff. This approach for adding new content to PATH is innovative because it leverages cumulative user feedback and automates the YouTube search process, making the PATH program highly scalable and easy to update.

**Review of successful web-based PA interventions in adults with overweight/obesity**

Several studies have employed web-based programs to promote PA in overweight/obesity.[32–34] The Active Living Every Day-Internet intervention demonstrated increased step count vs. no change in control group,[34] while a study by Morgan et al. reported increased metabolic minutes.[32]Both studies were limited by small samples and high attrition rates.[32,34] Patrick et al. studied a larger sample (N=441) in a 1-year RCT using web-based learning modules to promote PA. The participants accessed the study website for less than half of the 52-wk study period. Self-reported PA increased by 16 min/day in the intervention vs. control group, with 30% overall attrition.[33] Most significantly, minorities and those with obesity (BMI ≥35.2 kg/m$^2$) were more likely to withdraw from the study.[33] These prior studies are promising, but the low intervention engagement and diminishing interest over time contributes to the reported small effect sizes.[35,36] Moreover, the mechanisms of action of these interventions are not always reported, e.g., only one of the 3 studies reviewed above evaluated changes in an established mediator of PA (self-efficacy), limiting our understanding of how the interventions work.[32] More recent studies have focused on improving users' experience and engagement in populations at high CVD risk. A web-based RCT focusing on Latinas used strategies that included goal setting, self-monitoring, problem solving and social support to promote PA.[37] Participants logged on the study website an average of 22 times (SD 28) over the 12-mo study period.[38] Log-in frequency and time spent on website were associated with meeting the PA Guidelines (35 vs. 20 logins; P<0.01) at 12 mo.[38] The attrition rate was low (13% for treatment vs. 7% for control) yet, despite the promising data, investigators observed suboptimal intervention effect on PA among those with higher BMI.[37]

Taken together, these studies depict paucity of data on the long-term efficacy of web-based PA interventions in obesity and other high-risk groups. Moreover, the studies evaluate cardiovascular outcomes using individual risk factors without considering the effect on total CVD risk score as recommended by evidence-based guidelines.[39,40] Evaluating the total CVD risk score is highly recommended in high risk populations because it can help detect the cumulative effects of multiple risk factors which is not appreciated when only individual risk factors are considered.[41] Our proposed project will address these gaps by deploying better approaches for promoting adherence to PA Guidelines in adults with obesity, and better assessment of CVD risk.

**Study team experience**

Our team is uniquely qualified to conduct the proposed study because we have extensive experience conducting lifestyle based RCTs and have worked together in developing and pilot testing the PATH intervention. The PI (Kariuki) is well trained in the conduct of RCTs via a diversity supplement on the SMARTER trial (PI, Burke), the NHLBI PRIDE program and his recent pilot RCTs. Dr. Burke, a world-renowned expert in adherence to lifestyle

modification, will advise on clinical trial administration and strategies to enhance protocol adherence. Dr. Gibbs, current chair of the American Heart Association PA Committee, has conducted NIH funded studies on reducing sedentary behavior. She will advise on PA monitoring/measurements and coaching. Dr. Erickson, a member of the 2018 PA Guidelines Advisory Committee, has conducted highly mechanistic studies examining multiple mediators for the effects of PA on various health endpoints. He and Dr. Kariuki have collaborated on several grants including a recent R35 (PI, Erickson) examining mechanisms of action of PA on brain and cardiovascular health. He will advise on PA prescription and analysis of mechanisms of action driving changes in PA. Co-I Beatrice, the study dietician, is an instructor at Pitt with extensive experience implementing behavioral RCTs. Mr. Ogutu, founder of Ritiko LLC, has done all programming work on the PATH platform. Previously, he was a software Engineer at Google Inc where his assignments included optimizing the Google Search Engine and programming Android Operating System's support libraries.[42] He will be the project's systems engineer. Dr. Sereika has been a lead biostatistician on several NIH funded studies focusing on chronic diseases. She has worked with the PI in the SMARTER trial and the pilot studies informing this proposal and will direct all the statistical work for this study.

**Preliminary studies**

**Study 1**. We conducted 4 focus groups of African Americans to explore their PA barriers and preferences. The sample (N=26, 30-65 yrs) was 62% female with obesity (BMI, 32.2±5.4 kg/m$^2$). Consistent with prior studies conducted in white samples with obesity,[11,12,19] our focus groups expressed interest in PA programs that featured: a) people they could relate to; b) flexible schedule; c) stigma free environment; and d) enjoyable activities.[17] The participants opined that seeing "s*omeone that resembles our shape… doing the same program and struggling, that would really help."* They emphasized the need for a flexible program for busy people like "*working moms, especially if you have children and may not have support."* They also discussed body image concerns and the stigma they experience in public spaces. Younger participants (30-45yrs) viewed weight-loss as a vital motivator for engaging in PA while the middle-aged (45-65yrs) focused on health benefits of PA. The participants opined that when weight-loss is their focus, lack of progress discouraged participation in PA.[17] When we showed the focus groups sample workouts featuring some of their preferences, one man captured the prevailing sentiment with a comment on a diverse group cardio workout, "Y*ou got these people who are not as in shape so they kinda struggle doing it and then I'm like, I look just like them. I have no rhythm. They don't, this is fantastic for me!"* Implications for the proposed study: These data reflect the SCT[43] proposition that successful performance of a behavior by a model with perceived similarity to a person can help demonstrate strategies needed for one to succeed. The data informed the selection of 96 workout videos that we initially vetted and curated on PATH.

**Study 2**. After developing the beta version of the PATH website, we conducted a 12-wk pilot study to assess the technical readiness and usability of the platform and to develop an algorithm that could automate the process of identifying new workouts that appeal to our target population. The participants, who were not part of the focus groups, were asked to watch 120 min of workout videos every wk and to rate each video on a 5-star scale, comment about its suitability, and report technical glitches. The sample (N=25, 54.3±9.5 yrs) was 81% female, with obesity (35.3±7.7 kg/m$^2$). On average, the participants self-reported visiting PATH website at least twice/wk (61%)

where they spent ≥10 min/visit (91%). Also, they thought the beta PATH website was appealing (70%) and easy to navigate (96%), and were very likely, on a scale of 0 (not likely) to 100 (extremely likely), to use the workouts for exercise (mean score 83.8±16.7). Objective tracking data revealed sustained engagement through 12 wks; participants visited the site 2,111 times, spending ~7.3 min/visit and provided 852 comments and 914 ratings on the workout videos in the PATH library (77% rated ≥3.5/5). We used these data to remove unpopular workouts (<3.5/5) and optimize PATH. Attrition was 11.5%. To keep the PATH platform up-to-date and aligned with user preferences, we developed the PATH Fresher algorithm that interacts with the YouTube recommender system[44] to identify new workouts that are likely to appeal to PATH users. The algorithm goes through all the workout videos watched within the PATH platform and identifies those highly rated by users. A browser is then launched in the background and each video is 'visited' by the algorithm. These visits activate the YouTube recommender algorithm, which then suggests more similar workout videos. Using this iterative method, PATH Fresher algorithm computes a list of top recommended workouts such that each time a video is recommended by YouTube, it commands a +1 vote that is tabulated by PATH Fresher. Ergo, workouts that are recommended more often have higher votes. This list of recommendations is aggregated in the PATH back-end for vetting. Implications for the proposed study: The study provided critical data about the technical readiness, navigability, and user-friendliness of the PATH platform. The average ratings were used to deploy the newly developed PATH Fresher algorithm to identify new workouts that were vetted to increase PATH library to the current 112 workouts.

**Study 3**. After further optimization of PATH, we conducted a 12-wk pilot RCT to test feasibility and preliminary efficacy of PATH in a diverse sample of adults with overweight/obesity. The participants (N=82), who were naïve to PATH, were randomized to either PATH treatment (n=41) or a wait-list control (n=41) group. The PATH group was granted access to PATH website, met with a remote coach twice/mo, and rated perceived exertion (via the RPE Scale), favorability (via a 5-star scale), and suitability (via comment box) of each workout they used. The control group received the *Be Active Your Way* booklet,[45] and twice/mo newsletters on general health. MVPA was monitored via waist worn Actigraph GT3X for 7 days at baseline and at the end of the study, while daily steps were monitored via Fitbit Charge 2. After 12 wks the control group crossed over.

We screened 432 individuals, enrolled 82 (over 6 mos) and retained 96.3% (1 dropout, 2 withdrawn). The sample (N=82, 55.9 ±8.2 yrs) was 57.3% white, 80.5% female, with obesity (BMI 35.5 ±6.2 kg/m$^2$). Nearly all intervention participants accessed the PATH website at least twice/wk (92.1%), spent ≥10 min/visit (89.5%), and reported that the site was very appealing (68.4%), navigable (97.4%) and culturally appropriate (79%). When asked "*What did you like most about the PATH website?*" diverse workouts, convenient access, and tracking of progress were identified as the favorite aspects of PATH. There was sustained intervention engagement, with users providing 1,030 RPE ratings (78% ≤14), 974 favorability ratings (84% ≥3.5/5 stars), and 2,022 comments on the workouts (e.g., *"Friendly stretching routine. I appreciate a leader who is not the quintessential body type").* About 96% of the sample attended ≥5 of the 6 coaching sessions. The PATH Fresher algorithm

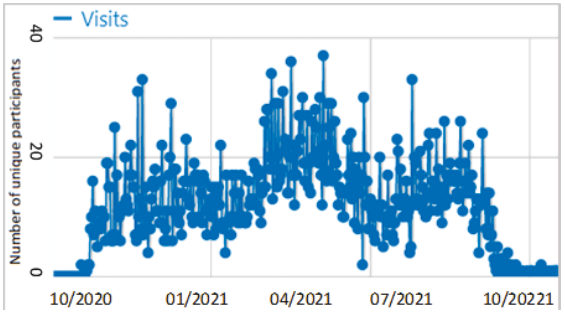



**Fig 2. Total visits on PATH website by the PATH group**

identified 1,781 new workouts that will be vetted for inclusion on the PATH website. Objective tracking via PATH web analytics revealed sustained engagement throughout the study period (Fig 2), with participants in the PATH group visiting the site 5,218 times where they spent an average of 7.5 mins per visit.

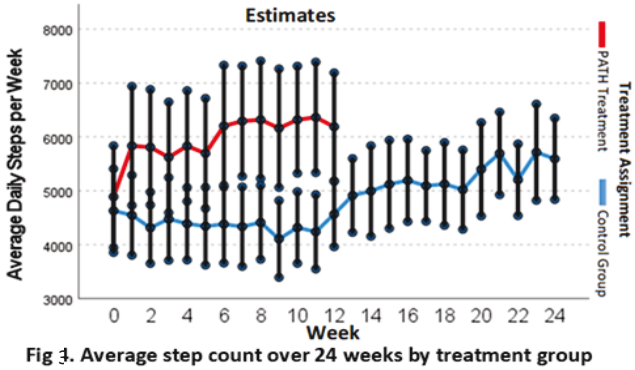



**Fig 3. Average step count over 24 weeks by treatment group**

In the adjusted analyses, we controlled for sex, race, age, walkability, and any adverse events or technical issues reported when examining PA and PA adherence. At 12 wks, the PATH group had greater mean changes in weekly MVPA (+58.9 vs. +0.9 min, p=.024) and daily steps (+1,246.4 vs. -64.2 steps, p=.002) compared to the control group. No between-group differences were detected for PA adherence over time, but the proportion of the sample that adhered to the PA guidelines increased in the PATH group (0.22±0.10, p=.041) compared to no improvement in control group (p≥.05). The average daily step count, collected over the initial 12-week period, demonstrated improvements in the PATH group vs. no change in control over time (Fig 3). After 12 wks, the treatment group exited the program while the control group crossed over to use the PATH intervention. All except one participant (n=40) crossed over and used PATH for 12 wks. Their average daily step counts improved consistent until their follow-up was complete at 24 wks (Fig 3). When examining the change in weekly average steps over 12 wks using group-based trajectory analysis, we identified 4 distinct trajectory groups: extremely low (25.5%), low (36.1%), moderate and linearly increasing (33.1%), and high but curvilinear decreasing (7.3%). Diagnostics support the adequacy of this 4-group model (Fig 4). There were no between-group differences for change in CVD risk factors over time, but PATH group showed significant within group improvements in weight (-3.2±1.5, p=.043), waist circumference (-1.0±0.4, p=.010), body fat (-0.9±0.3, p=.004), and a trend in systolic BP (-4.2±2.2, p=.057).

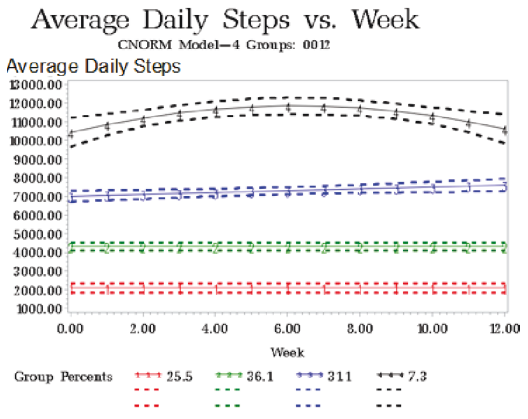



**Fig 4. group-based trajectory: weekly average steps**

No significant changes in CVD risk factors were observed in control group (all p≥.05). We did not expect to see any changes in HbA1C, lipids or total CVD risk score within 12 wks. We did the lab tests to pilot the logistics of remote sample collection. All PATH effects were similar by race and sex. There were no major adverse events. Minor events (n=27) such as mild COVID-19 were similar in PATH (48%) vs. control (52%) groups (p=0.06). mImplications for proposed study: This pilot RCT demonstrated the PATH intervention is feasible and acceptable, and provided compelling evidence of preliminary efficacy in promoting PA and reducing CVD risk in our target population. The proposed study will examine the efficacy of PATH intervention in promoting adherence to the PA guidelines.

## 4. Study Endpoints

**Indicators of PATH Fresher algorithm's effectiveness in identifying workout videos that match specific user preferences (aim 1).** Effectiveness of the PATH Fresher algorithm will be indicated by its ability to analyze PATH users' data, spin up new browser sessions in the background to activate the YouTube recommender system, and select workouts that will be highly rated by target users (≥3.5/5 stars). Systems Usability survey (SUS) will be used to evaluate the overall satistaction with the PATH platform.

**Acceptability of the disseminated educational resources focusing on improving diet quality (aim 2).** The resources will be curated from an extensive library of standard behavioral treatment (SBT) content previously developed and validated by Co-I Burke. Their acceptability will be evaluated via a researcher developed end of study survey. The Healthy Eating Index (HEI) will be used to assess diet quality at baseline and 6 months. Researcher developed end of study survey will be used to assess satisfaction with diet and other resources disseminated via the PATH platform.

**Measures of PA and adherence to PA guidelines (Aim 3).** The efficacy of PATH in enhancing adherence to PA Guidelines will be evaluated at 6 mos using MVPA data collected via ActiGraph GT3X, worn on the waist for 7 days at 6 mos. Adherence to PA Guidelines will be defined as achieving ≥150 min of MVPA/wk. Percent change in adherence will be calculated as: [(Post-intervention MVPA - Baseline MVPA)/Recommended MVPA×100]. For instance, if Mary in Box 1 attained 140 MVPA min/wk at 6 mos, her % change in adherence is: (140-90)/150×100=33%. Between group difference in % change in adherence and proportion of individuals who attain the recommended MVPA will be evaluated. ActiGraph GT3X+ is a research-grade accelerometer validated to provide objective measures of PA in free-living conditions.[46] Established and novel methods will be used to process ActiGraph data which will be considered valid if ≥4 days with ≥10hrs of wear time are measured.[46] Freedson cut points will be used to classify MVPA (≥1952 cpm),[47,48] and MVPA will be operationalized as bouted (MVPA accumulated in bouts of ≥10 min, with allowance for 2 mins below the threshold) and unbouted (all min) reflecting current research recommendations.[49] Non-wear time will be 60-min periods of continuous 0 cpm allowing for ≤2 min of ≤100 cpm.[50] Although waist worn Actigraph GT3X is associated with better PA estimation,[51] its long-term use is associated with low adherence to self-monitoring of PA.[52] Therefore, sustained PA engagement will be evaluated via Active Minutes data collected via Fitbit Charge 5 and will be analyzed via the adherence strategy described above. Fitbit Charge 5 is a triaxial accelerometer worn on the non-dominant wrist using a 24hr wear protocol. Validation studies suggest that Active Minutes, measured by Fitbit's proprietary algorithm, may slightly overestimate MVPA[53–55] but the device is ideally suited for long-term self-monitoring due to its user friendliness and extensive use in RCTs.,[56] including SMARTER RCT.[57] Similar to other studies,[53] Fitbit wear time will be calculated using the step based algorithm. Any minute when steps are greater than zero will be categorized as wear time. Non-wear time will be identified as bouts of 60 consecutive minutes with zero steps.[55] We will subtract non-wear time from 24 hours to calculate total daily wear time. A week will be considered valid if ≥4 days with ≥10hrs of wear time are measured.

**Measures of cardiovascular outcomes (Aim 4).** Cardiovascular outcomes will be indicated by change from baseline to post-intervention in CVD risk score calculated using the 2013 Atherosclerotic Cardiovascular Disease (ASCVD) Risk Calculator.[58] The algorithm provides sex and race-specific estimates for the first CVD event for black and white men and women. The scores range from 0-100% with higher scores representing poor

cardiovascular health status. The composite risk factors included in the algorithm are age, total and HDL cholesterol, SBP (including treated/untreated status), diabetes and current smoking status, and will be measured using the protocols outlined under baseline assessment. The main outcome will be between group difference in risk score change computed as: (end of study score – baseline score). We will also employ the same strategy to evaluate changes in independent risk factors for CVD (secondary outcomes): waist circumference, weight, BP, Life's Essential 8™, HbA1C, adiponectin, and lipids (total, LDL, HDL cholesterol). Because diet quality can have a major impact on CVD risk, the relation between the PATH intervention and CVD risk will be adjusted for diet quality which will be described via the HEI. The CVD risk factors, and HEI are measured using protocols described earlier. At the end of study, the optional Early Childhood Adversity Survey (ACES) will be used to identify early life experiences that may impact the study outcomes.

## 5. Study Intervention/Investigational Agent

The health coach, who will be a member of the study team, will provide each participant with a password-protected profile to access the PATH website, and a detailed orientation on how to use all the resources included in PATH. In addition, the health coach will meet remotely with each participant twice/month. The proposed PATH intervention will counsel and guide participants in the development of multiple behavior change strategies that will facilitate and support them in making changes in their lifestyle and PA habits to support long-term adherence to the minimum threshold of PA Guidelines (150 MVPA mins/wk). In our 12-wk feasibility study, the PATH intervention group increased weekly MVPA by 58.9 mins. We will employ the piloted strategy to promote adherence to the PA Guidelines. We will integrate the Fitbit API with our PATH platform. This will enable us to capture longitudinal trends in PA and to display the progress towards PA goal on each participant's dashboard. The coach will work with each participant in the treatment group to develop their PA prescription guided by the FITT-VP principle[59] which recommends the frequency, intensity, duration, type, volume and progression of PA. Although there are no established standards on how to increase PA , available evidence suggests it is safe to increase MVPA by 10 min/wk,[60] which translates to 3,270 steps/week.

The coach will work with each participant to develop a tailored plan geared towards increasing MVPA by ~10 min/wk (3,270 steps/week) with each coaching encounter. Given the scheduled 12 coaching encounters during the 6 mos study period, participants at all levels of fitness will have a chance to develop a PA regimen that is adherent to the PA Guidelines. Participants with relatively high baseline PA will target the higher threshold of the PA Guidelines (300 MVPA min/wk). Our PA prescription process will begin by identifying a suitable PATH level for each participant based on their estimated maximum rate of oxygen consumption during incremental exercise ($VO_2$ max).[59] The $VO_2$ max will be predicted using a validated non-exercise prediction model for peak $VO_2$ whose covariates include sex, age, waist circumference, resting heart rate and PA index.[61] Individuals with predicted $VO_2$ max ≤ 35$^{th}$ percentile for their age and gender will be considered for assignment to the Beginner PATH level (includes light intensity PA [<3 METs]). Those with $VO_2$ max above 35$^{th}$ percentile rank will be assigned to Intermediate PATH level which includes moderate intensity workouts (3-5.9 METs) in addition to the Beginner PATH content. Based on our pilot experience, no participant will be assigned to begin at the Proficient PATH level which includes vigorous intensity workout videos (≥6 METs) in addition to the Intermediate PATH content. Rather, participants will be given access to the level based on their RPE scores at the intermediate level and

coach evaluation. The coach can change PATH level based on their assessment of participant's capabilities during the meetings.

After assigning the PATH level, the health coach will guide each participant in selecting their weekly PA goal and will help them start slowly with a plan to establish regular exercise frequencies of 3-5 days per wk. The coach will also guide participants to select activities with intensity to help them progress along the PA continuum (i.e., from inactive to light PA and then MVPA). To foster safety, participants will be instructed to use the RPE Scale[62] as a guide for adjusting the intensity of their PA regimen. The scale ranges from 6 (no exertion at all) to 20 (maximal exertion) and is embedded within each workout video on PATH. The coaches will also help participants set-up Fitbit safe heart rate zones based on their fitness levels, with a goal of progressing to the Cardio Zone (70% and 84% of maximum heart rate) by the end of the study.

Participants will be asked to use workouts that elicit perceived exertion ratings between 12 to 14 (i.e., moderate intensity) on the RPE Scale. The coach will review progress made every 2 wks. More intensity will be allowed, including transition to the next PATH level, when most workouts within the assigned PATH level are perceived to be "fairly light" (≤11 on RPE Scale). If a participant forgets to rate their workouts, they will be reviewed during the coaching session and a goal that aligns with each person's capabilities recommended. This method will ensure the prescribed regimen is based on ability and fitness status. Although the health coach will provide solid examples of the workout videos that could help participants attain their personalized goals, each participant will have access to all resources within their PATH level and will be encouraged to select a regimen that includes their preferred workout videos and other types of PA appropriate for their fitness level. The workouts that are recommended by the health coach and those selected by each participant as favorites will be featured on the personalized PATH dashboard. Box 1 illustrates a PA prescription for Mary; in the first 2 wks, her PA regimen included her usual walks (90 MVPA min/wk) and 10 min of additional dance workouts each wk. The PA prescription will be revised during the virtual meetings with the coach to reflect the progress made towards the study goal. Those who attain adherence to the PA Guidelines within the first 6 mos will achieve the study goal and their plan for the remaining 6 mos will be to maintain the improved PA regimen. However, each participant can opt to continue with a gradual increase in PA volume and/or intensity.

**Box 1. Mary's PA prescription using the FITT-VP principle**

Mary is a 45-year-old woman with a $VO_2$ max of 32.8 (40$^{th}$ percentile). Her baseline MVPA is 90 min/wk mainly derived from walking for 20 min twice/week. She prefers to ↑ her PA by using dance workout videos. The PA coach will assign Mary to the Beginner PATH based on her $VO_2$ max, and work with her to develop a plan to ↑ her PA with a goal to attain the 150 MVPA mins/wk recommended by the Guidelines:

- ✓ Gradually increase PA **frequency** (e.g., an additional session of PA every 2 wks)
- ✓ Set limits for PA **intensity:** start with workouts that she can do at perceived exertion ratings between 12 to 14. The progress will be reviewed every 2 wks, with more intensity allowed when most workouts within the assigned PATH level are perceived to be "fairly light" (≤11 on the RPE Scale).
- ✓ Gradually ↑ the **time**. Her PA regimen duration can be increased by 10 min with each coaching encounter for the first 6 months, then maintain the increased PA.
- ✓ Recommend workout videos with **types** of PA that align with her goals. The coach will recommend specific workouts that can help Mary attain her goals, but she will have an option to select her favorite workouts within established safety parameters.
- ✓ Flexible strategy for attaining desired PA **volume**. Mary can attain the desired volume of weekly PA by either ↑ her routine walks or via her favorite workouts.
- ✓ Evaluation of **progress.** The coach will have a zoom meeting with Mary twice a month during the first 6 months to review & revise PA prescription based on the progress made. After 6 months, coaching will be monthly and focused on either maintaining her PA regimen at 150 MVPA min/wk or continue to increase her PA.

To simplify access and support maintenance of PA, the workout videos are organized in categories (e.g., walking, dance, steps aerobics) and can be sorted by duration and METs. To reduce risk of injury, the amount

and intensity of PA will be increased gradually, with emphasis on duration followed by intensity per the American College of Sports Medicine.[59] The coach will also teach safety precautions including foot wear and hydration. To complete PA prescription, the participants will suggest their preferred schedule for receiving motivational PA reminders, which will automatically be sent as text messages and/or emails from the PATH platform ecosystem motivating the user to log on to PATH and do their workout (e.g., *It is time for your workout! No matter how slow you go, you are already beating everyone sitting on the couch — S. Miller*). The short motivational messages are randomly selected from a bank with >250 vetted messages, which will be updated before beginning of the study. Also, we will ask the participant to provide a schedule for the Zoom meetings with a health coach to monitor progress and revise PA goals. During the study, we will encourage participants to adhere to their PA goals and share their experiences on the PATH community forum. An end of study survey, developed by the study team, will capture feedback on participant experiences and the most helpful PATH resources.

***The control arm.*** After randomization, a study staff will have a zoom meeting with each control group participant where they will be advised to use their tracker and Beactive Your Way Guide so as to keep the contact between the groups as similar as possible.

***Protocols for both treatment and control arms.*** During the twice/month meetings with intervention and control groups, the study staff will supervise BP measurements and will ask the participants to step on the scale. These data will be used to monitor BP, weight and body composition trajectories. To minimize participants' burden, both the intervention and control arms will receive an email with a brief PDF addressing one diet component every 4 wks. The diet information will also be available to them as modules on our research website. At the end of the study assessment, both control and intervention group participants will be given option to continue using the PATH platform at their convenience without any contact with the coaches. The verbal consent for continued participation will be documented on REDCap.

## 6. Procedures Involved

***Study design.*** *We propose* a 6-mo parallel RCT with 88 participants randomized 1:1 to either the PATH intervention (Table 2) or attention control group. The staff conducting the assessments will be blinded. This change has been informed by the need for the investigators to promptly evaluate all the events the participants report to the study staff. To date, no reportable adverse events have occurred, but participants have been informing our staff when they go for elective procedures or when they have health emergencies such as food poisoing. The staff document the details of all reported events and the PI reviews them to make a determination on what is reportable. This data is shared with Dr. Gary, the NIH appointed safety officer. The primary endpoints are moderate-to-vigorous physical activity and step count at 6 mos.

***Setting.*** We will conduct the study at Emory University and recruit participants primarily from the Atlanta metro region. We will seek Institutional Review Board approval and a written informed consent from all participants prior to participation in study procedures.

***Participants.*** Eligibility criteria: regular access to the Internet, age ≥18 years with no upper limit, BMI ≥30kg/$m^2$, successful self-monitoring of PA (≥4 days with ≥10hrs wear time) via waist worn Actigraph, and non-adherence to the PA Guidelines (<150 min of MVPA/wk). Exclusion criteria: pregnancy or intention to become pregnant within 6 months, mobility restrictions, or any condition that requires supervised PA (e.g., stroke). Individuals with history of heart disease, diabetes, or those who respond in affirmative to any question in the Physical Activity Readiness Questionnaire will be required to obtain PCP clearance before enrollment.

***Recruitment.*** To obtain our target sample (88) we will use resources available to Emory investigators, including Georgia Clinical and Translational Science Institute, ResearchMatch (free registry of research volunteers), electronic mailings, announcements on social media sites, and fliers posted in the community. We also will recruit from primary care practices affiliated with Emory Healthcare. We will aim to recruit a diverse sample that includes ≥25% males and ≥30% minorities.

***Screening and online questionnaires.*** Individuals who respond to recruitment solicitations will be directed to a web link that provides a brief overview of the study and eligibility criteria. Those who are eligible will be guided to click a link to complete a battery of 9 brief questionnaires which are outlined with their validation references in Table 1 (used in recent pilot studies). We transferred the questionnaires to the REDCap platform so they can be completed online in one or multiple sittings within 30 mins. Data from the questionnaires will be used for eligibility screening and to examine the impact of sleep disturbance, health status, stress, and risk of depression on study outcomes. The eligibility criteria are embedded within the online surveys so that the data collection is terminated when a potential participant enters information that makes them ineligible (e.g., history of stroke). Those who complete the RedCap questionnaires will be asked to complete one dietary recall using the Mediterranean Eating Pattern for Americans (MEPA) Questionnaire[63] and scheduled for a 20-min phone interview, during which the dietary recall will be reviewed and Behavioral Risk Factor Surveillance System (BRFSS)Physical Activity Questionnaire [64] administered to review PA patterns. Those with <150 min of MVPA/wk will be scheduled for a 15-min technology set-up phone call.

***Technology set-up, informed consent, mediation, and diet assessment.*** Prior to the phone call we will provide potential participants email instructions on how to install Zoom (for assessments/coaching), Withings (weight, BP) and Fitbit (PA) apps. During the phone call, the study staff will verify software installation and provide login credentials for Fitbit, Actigraph and Withing apps. We employed this strategy in our recent pilot RCT where 82 participants self-installed these apps with minimal problems. During the phone call, study staff will review the study procedures and commitments. Those still interested in the study will receive a copy of the informed consent to review and sign via REDCap. Those who consent will be asked to complete All of Us Research Program Lifestyle Survey (smoking and alcohol), exercise self-efficacy,[65] self-regulation,[66] PA enjoyment,[67] social support,[68] and outcome expectancy[69] questionnaires. The 5 validated questionnaires (Table 1) are frequently used to examine mediators[65–69] that are known to influence PA and cardiovascular outcomes.[70–73] The questionnaires can be completed in REDCap within 30 min and will be repeated at 6 mos. An optional Adverse Childhood Experiences (ACEs) questionnaire will be used to explore difficult childhood experiences that may be affecting the variables of interest to the study. The participants will be asked by the study staff to give their verbal consent to receive this questionnaire at the end of study assessment.

***Baseline assessment via Zoom.*** Those who are eligible will be scheduled for a baseline assessment via HIPAA compliant Zoom. We will employ the strategy that we have successfully piloted in our feasibility studies. Before the assessment, each participant will receive a shipment with all supplies including dry blood spot kit, Fitbit Charge 5, Actigraph GT3X, Withings Arm BP Monitor, Withings scale, Perfect Waist Tape Measure, stretch band and an optional tablet holder for those who prefer using phones. During the Zoom visit, the study staff will review the data in the PA readiness questionnaire (PAR-Q+) [74] to ensure that individuals who need PCP clearance obtain it before they are randomized to a treatment condition. In our pilot work, we used a HIPAA compliant online Fax (https://www.srfax.com) to send and receive the clearance forms to and from PCPs on behalf of participants.

| Questionnaires and scheduled assessments | Baseline | 24wks |
|---|---|---|
| **Screening, Health History and Lifestyle Questionnaires** | | |
| Sociodemographic and Medical History Questionnaires | X | |
| PA Readiness Questionnaire (PAR-Q+)[74] | X | |
| Paffenbarger Exercise Habits Questionnaire[75] | X | X |
| Barriers Self Efficacy Scale[76] | X | X |
| PROMIS SF Sleep Disturbance Questionnaire[77] | X | X |
| PROMIS SF Sleep-Related Impairment Questionnaire[77] | X | X |
| Center for Epidemiologic Studies Depression Scale[78] | X | X |
| NIH Toolbox Perceived Stress[79] | X | X |
| EQ-5D health status instrument (EQ-5D-5L)[80] | X | X |
| **Questionnaires Measuring PA and Potential PA Mediators** | | |
| Mediterranean Eating Pattern for Americans Questionnaire.[63] | X | X |
| BRFSS Physical Activity Questionnaire[64] | X | X |
| All of Us Research Program Lifestyle Survey (smoking/alcohol) | X | X |
| Exercise Self-efficacy Scale[65] | X | X |
| Self-regulation Questionnaire[66] | X | X |
| Physical Activity Enjoyment Scale[67] | X | X |
| Social Support for Exercise Scale (SSES).[68] | X | X |
| Multidimensional Outcome Expectations for Exercise Scale[69] | X | X |
| **Medication History and Cardiometabolic Assessments** | | |
| Medication History | X | X |
| Zoom supervised self-administered blood pressure | X | X |
| Zoom supervised self-administered weight | X | X |
| Zoom guided self-administered waist circumference | X | X |
| **Notes:** $VO_2$ peak: Men = 100.27-(0.296*age) -(0.369*waist circ) - (0.155*heart rate) + (0.226*PA - index); Women = 74.74-(0.247*age)-(0.259*waist circ) - (0.114*heart rate)+(0.198*PA-index)[61] | | |
| • HbA1C, adiponectin, lipids (total, LDL and HDL cholesterol) | X | X |
| CVD risk score computed using ASCVD Risk Calculator.[81] | X | X |
| Heart Health Score computed using Life's Essential 8™ data | X | X |
| American Diabetes Association Risk Score[82] | X | X |
| Fitbit charge 5 data on PA (continuous) | X | X |
| Actigraph GT3X accelerometer data on MVPA (7 days) | X | X |
| **Users' Feedback** | | |
| Likert scales and post-intervention survey | | X |

The assessments will commence with the study staff reviewing the waist circumference self-measurement video and guidelines developed by the International Chair on Cardiometabolic Risk.[83] The staff will instruct the participant to go to a private location where they can measure their waist on bare skin using the Perfect Tape Measure. The participant will show the locked tape measure to staff via the camera. There is evidence for strong correlation coefficients (0.8 to 0.9) between self- and technician-measured waist circumference.[84–88] The video is available here: (http://www.myhealthywaist.org/index.php?id=90). The staff will instruct the participant to wear light clothing and with bare feet, stand on the smart scale footpads to measure weight, percentage body fat, percentage body water, muscle and BMI. The study team can access the recorded measures via Withings API.

We will use the clinically validated Withings Arm BP Monitor for self-measurement of BP**.** The monitor has a one-touch easy to read digital screen, and a cuff that fits an arm circumference of 22-42cm (larger cuffs available on request). Staff will instruct the participant to apply the cuff on the bare left arm, then sit in a chair with both feet

resting flat on floor and back straight and supported. After 5 mins rest with the left arm resting on a flat surface at heart level, participants will be asked to turn on the BP machine and take 3 measurements at one-minute intervals and show the BP to the staff. Participants with 2 readings of elevated BP (>130/80) will be referred to their PCP, with a request to update us if treatment is initiated. Those with severe hypertension (BP ≥180/110 mmHg) will be asked to seek urgent medical attention before their eligibility can be re-evaluated. Those without PCPs will be given the contact of free health clinics in Atlanta metro and asked to seek medical care before eligibility is re-evaluated. Blood samples for HbA1C, Adiponectin, LDL, HDL, and total cholesterol will be collected via dry blood spot kits. Study staff will supervise participants performing the fingerstick sample following the steps outlined in the sample collection video/instructions provided by the test kit manufacturer. The samples will be mailed by each participant to the lab using the included return address. These samples will be processed in the lab for analysis using established protocols for dry blood spot method. Staff will refer individuals with HbA1C levels >6.5 to their PCP or free health clinic for further evaluation and management. Research staff blinded to treatment assignment will repeat these assessments at 6 mos.

***Run-in period***. At the end of baseline assessment, the staff will instruct participants to wear the ActiGraph GT3X on their waist and Fitbit on their wrist to monitor PA for a 7-day run-in period. The run-in period will help potential participants appreciate study expectations and will provide objective data on baseline MVPA. Individuals will need to wear Fitbit and ActiGraph for ≥10 hours on ≥4 days to be eligible.[51]Those eligible will be randomized to either the treatment or attention control group. In our pilot study all participants met the required ActiGraph wear time.

***Randomization and orientation.*** After completion of the run-in period, non-blinded staff will randomize eligible participants with equal allocation (1:1) to either the PATH intervention or the control arm using a computer software. Group assignments will be generated via REDCap randomization scheme to achieve a balance between the treatment and control groups in regard to age (18-45; 46-64; ≥65 years), sex (male/female) and race (white/minorities). After randomization, a study staff will meet with each participant within 7 days for 30-min on Zoom to orient him/her to the resources of their randomized group. Participants in both groups will be asked to wear Fitbit Charge 5 on their non-dominant hand for the entire duration of the study using a 24hr wear protocol. They will be asked to contact the project manager, if need be, outside the limited scheduled times.

***Procedures involved in the continued use of the PATH platform:*** After the completion of the study participants will be given the option to continue using the PATH platform without having any contact with the coaches. Each participant will maintain their current login credentials (i.e., username, password) and profile. Those who wish to update their profile with a new username or email will be requested to reconnect their trackers (Withings scale and Fitbit traker) with the study website via the tokens generated by Fitbit and Withings if they would like to continue seeing their daily progress. Those who fail to reconnect the trackers can still use the platform, but will not be able to see their progress. After the profiles are updated, the participants will use the videos on the PATH platform at their own pleasure. They will be encouraged to continue wearing their trackers and stepping on their scales, but they will not be required to do so. The authorization to access the participants' tracker data will be renewable annually. The annual plan will conform with Withings and Fitbit requirements to get users reauthorize access to their data via API interface every 12 months. No additional procedures will be added.

## 7. Statistical Analysis Plan

**Sample Size Justification.** The total sample size of 88 enrolled and randomly assigned (44 per treatment group) was determined considering 1) the anticipated effect sizes of the PATH intervention focusing on the primary more distal outcomes (Aims 3 and 4) informed by the relevant literature and recent pilot work, 2) the testing of multiple hypotheses at the key study time points, and 3) the anticipated participant attrition over the 6-month follow-up period. Regarding possible efficacy of PA interventions in terms of adherence to PA guidelines (Aim 3), Hartman, et al.[90] observed a large odds ratio (OR) of 3.29 for adherence to ACM guidelines at 6 months between a tailored PA internet intervention (n=104) and wellness contact control internet (n=101) groups with maintenance of adherence to ACM guidelines in the PA intervention group at 12 months in 205 inactive Latinas. Furthermore, the study reported small to moderate differences between the intervention and control groups with respect to self-reported MVPA at 12 months (mean diff.=30.68, SE=11.27, p=.007; d= 0.38), with most of the improvement in PA occurring during the 6-month PA intervention period. Regarding differences in effects for CVD risk factors (Aim 4), Arija, et al.[91] detected significant differences between the control (n=55) and PA program (n=152) groups on CVD risk scores (d= -0.426, p=.032) and SBP (d= -0.480, p=.002) with trends for weight reduction (d= -0.295, p=0.059) at 9-months follow-up. With these results from the literature in mind and with at least 44 participants per treatment group (88 total), we would have at least 80% power to detect small to medium effect sizes for the efficacy of the PATH intervention on PA, i.e., mean difference of 20 mins of MVPA or 13.3% absolute change in terms of adherence to PA guidelines (Aim 3), and CVD risk factors, in terms of the CVD risk score (Aim 4), at 6 months when using linear contrasts from either linear or generalized linear mixed modeling at testwise (Bonferoni-adjusted) significance level of .05. Given our repeated measures study design, we anticipate some participant attrition. To ensure sufficient sample size with complete assessment through 6-months follow-up, we plan to enroll 88 participants (44 per treatment group) retaining at least 76 participants (38 per treatment group) assuming a 15% attrition through the 6-month follow-up based on attrition rates observed in the literature.[92] In our 3 month pilot study, the attrition rate was 4.6%.

**Statistical Analysis.** Data will be analyzed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC) to conduct exploratory data analyses for data screening, including missing data assessment; repeated measures modeling; and modeling of attrition. M*plus* (version 8.8, Muthén & Muthén, Los Angeles, CA) will be used for mediational analyses to explore possible mechanisms of action of the PATH intervention. Data will first be carefully screened with the results of these preliminary analyses informing the final analysis strategies to be applied to address study aims and exploratory analyses. Although hypotheses are stated as directional, hypothesis testing will be non-directional with the significance level set to 0.05 and confidence interval estimation at 95%, unless otherwise specified. Sex as a biological variable will be considered in secondary analyses as a possible covariate or treatment modifier of the efficacy of the PATH intervention.

*Preliminary Analyses*. Exploratory data analyses will be used to screen for data anomalies and to describe data based on key design elements (e.g., group, time, group by time). We will use data screening results to 1) describe data distributions; 2) identify associations between variables, including possible group imbalances; 3)

evaluate amounts and patterns of missing data; and 4) check for violations of underlying statistical assumptions of the planned analyses. If assumptions are seriously violated, we will consider data transformations or apply more robust statistical methods. If sparse categories/cells are encountered, we will meaningfully collapse categories or apply exact estimation methods. Regarding the missingness of data, we will study participants who have dropped out or have incomplete data to detect any distinguishable characteristics. The randomness of missing data will be investigated using information on participant characteristics to help discern patterns in the missing data, identify possible missing data mechanisms, and inform strategies to handle missing data. If data are ignorably missing, the likelihood-based estimation procedures to be used, linear or generalized linear mixed modeling, will produce unbiased parameter estimates while allowing us to retain observations with missing values on the outcome variables. If data are not missing at random, we will apply multiple imputation and two extreme case scenarios (worst/best case) to address missing data. As needed, multiple imputation will be used to impute missing values on covariates/predictors. If nonrandom missingness is suspected, we will use selection or pattern mixture modeling to explore the sensitivity of results to the assumed missing data patterns.

**Analysis Strategy for Aim 3: To evaluate the efficacy of the PATH intervention on improving adherence to the PA Guidelines.** An "intent-to-treat" (ITT) approach will be used to test the efficacy of the PATH intervention on the distal outcome of adherence to the PA guidelines **over time.** All participants will be analyzed as randomized, regardless of protocol adherence, intervention received, withdrawal, or protocol deviations. We will explore the sensitivity of the results assuming ITT to examine the impact protocol deviations on the PATH intervention efficacy. Since key study endpoints are assessed at multiple time points, repeated measures modeling (e.g., linear or generalized linear mixed modeling methods and/or marginal modeling using generalized estimating equations as appropriate, both assuming a normal error structure) will be used to test the efficacy of the PATH intervention on the measures of adherence to the PA guidelines over time (baseline [0], and 6-months [long-term] follow-up). The primary independent variable is randomized treatment group assignment (PATH vs. attention control). Fixed and/or time-dependent covariates may be included in models secondarily based on the preliminary analyses and literature (e.g., sex, race, age, hypertension treatment, diet quality) and pre-randomization factors. Repeated measures modeling will be applied to the more distal outcomes of adherence to PA guidelines, where the primary outcome is **adherence to PA guidelines**, and **weekly MVPA and daily steps** are more secondary outcomes. Adherence to PA guidelines will be analyzed as 1) a continuous variable using linear mixed modeling assuming normally distributed model errors and 2) a binary variable (base on the threshold from the PA guidelines regarding MVPA) using GLMM assuming a binominal error with logit link. As possible, weekly MVPA and daily steps will be analyzed as continuous-type, ratio level outcome variables using linear mixed modeling assuming normally distributed model errors. In the event of the non-normality of residuals and normality cannot be induced through data transformation, outcome variables will be dichotomized using meaningful cut points and generalized linear mixed modeling applied assuming a binominal error and logit link. Initially, the structure of the estimated variance-covariance matrix for the repeated assessments of the particular outcome variable will be carefully examined for the total sample and by assigned treatment group to determine the appropriate variance-covariance structure. Standard fit indices (e.g., AIC, BIC) will be used to evaluate the repeated measures models estimated assuming different variance-covariance structures to identify

the most appropriate (i.e., "best fitting") variance-covariance structure. Time will be treated as a fixed, within-subjects factor, while treatment group will be entered as a fixed, between-subjects factor, with interactions between time and treatment group. Model assessment will entail residual analysis and an evaluation of influence diagnostics. Covariates (fixed and time-dependent) identified via preliminary analyses and the literature reviews, and pre-randomization factors will be considered secondarily in analyses. In particular, we will explore participant sex as a covariate and possible treatment effect modifier of the PATH intervention. Individual regression model parameters will also be computed and reported with confidence intervals. To test the hypothesis **(Aim 3, H1)** that **the PATH intervention group will have greater adherence to PA guidelines compared to the attention control group in the short- and long-term**, linear contrasts will be specified and estimated to compare **adherence to PA guidelines** between the treatment groups at 6 months relative to baseline values, respectively. The testwise significance level will be set to 0.05 (Bonferroni-adjusted). Point and interval (95% confidence intervals) estimates based on linear contrasts will also be computed as both unstandardized and standardized effect sizes of the short- and long-term efficacy of the PATH intervention.

**Analysis Strategy for Aim 4: To compare the effects of the PATH intervention on CVD risk factors.** A similar repeated measures modeling approach as outlined for Aim 3 will be utilized to evaluate the efficacy of the PATH intervention compared to attention control condition on the secondary and more distal CVD risk factors including CVD risk score (primary outcome), weight, blood pressure, waist circumference, HbA1C, and lipids at 6-months follow-up. The secondary outcomes of the identified measures of CVD risk are either interval or ratio scaled, and a normal error structure (or following a suitable data transformation) will be assumed when modeling. As necessary, generalized linear mixed modeling assuming a binomial error will be applied to model CVD risk factors dichotomized based on clinically meaning cut points. To test the hypothesis **(Aim 4, H2)** that **the PATH intervention group will have a greater reduction in CVD risk score vs. the attention control group**, linear contrasts will be specified and estimated to compare the treatment groups on the change in CVD risk scores at 6-months follow-up relative to baseline values at a testwise significance level of 0.05 and confidence interval estimation at 95%. As for Aim 3, covariates will be considered secondarily in analyses, including participant sex as a possible covariate and treatment effect modifier.

**Post-study statistical analysis:** For participants who opt to continue using the PATH platform, the study team will continue to have access to their data that is synched to the platform from their Fitbit tracker and Withings scale when they use them. We will do descriptive analysis to evaluate the login patterns and how they correlate with physical activity levels and body composition metrics. The data will help us explore the utility and sustainability of participants using the platform on their own without any help from the coaches. We will also evalute how they continue to rate the workout videos on the platform and use the data to improve the platform.

## 8. Data and/or Specimen Banking

All the blood samples collected for this study will be discarded after the analyses. There are no plans to store the specimens beyond the conclusion of the study. However, the data elicited from these samples will be included in the study dataset and may be shared with other investigators following the outlined data sharing plan.

### 9. Sharing of Results with Participants

Once the study has been completed, we will send each participant a summary of all of the results of the study and what they mean. We will not send individual results unless we find something of urgent medical importance to the participant. The study team will brief the participant on the abnormality detected and refer them to their PCP or free health clinic for further evaluation and management.

### 10. Study Timelines

The proposed study timeline is 12 mos. During the first 3 mos, we will optimize the PATH platform using recent pilot data, finalize the study protocol, obtain Institutional Review Board and Data and Safety Monitoring Plan approval, and finalize the recruitment strategies. We will also hire and train study staff. Study recruitment will commence from month 4-9, with a target to recruit 15 participants each mo. Since a rolling recruitment strategy will be adopted, assessments will continue concurrently with recruitment. In months 10-12, we will focus on finishing end of study assessments, data analysis and dissemination. Those who opt to continue using the PATH platform after their commitment to the study is over will be given access that will be renewable annually. The annual plan will conform with Withings and Fitbit requirements to get users reauthorize access to their data via API interface every 12 months. Even those who do not authorize our API access to their trackers will have the option to continue using the PATH platform, albeit without seing their progress, as long as the study team has the resources to maintain their access.

### 11. Inclusion and Exclusion Criteria

**Eligibility criteria:** regular access to the Internet, age ≥18 years with no upper limit, BMI ≥30kg/$m^2$, successful self-monitoring of PA (≥4 days with ≥10hrs wear time) via waist worn Actigraph, and non-adherence to the PA Guidelines (<150 min of MVPA/wk).

**Exclusion criteria:** pregnancy or intention to become pregnant within 6 months, mobility restrictions, or any condition that requires supervised PA (e.g., stroke). Individuals with history of heart disease, diabetes, or those who respond in affirmative to any question in the Physical Activity Readiness Questionnaire will be required to obtain PCP clearance before enrollment.

### 12. Population

- Adults unable to consent will be excluded
- Individuals who are not yet adults will be excluded
- Pregnant women will be excluded
- Prisoners will be excluded
- Cognitively impaired or Individuals with Impaired Decision-Making Capacity will be excluded
- Individuals who are not able to clearly understand English will be excluded

### 13. Vulnerable Populations

N/A

### 14. Local Number of Participants

To ensure sufficient sample size with complete assessment through 6-months follow-up, we plan to enroll 88 participants (44 per treatment group) retaining at least 76 participants (38 per treatment group) assuming a 15% attrition through the 6-month follow-up based on attrition rates observed in the literature.[92]

### 15. Recruitment Methods

To obtain our target sample (88) we will use resources available to Emory investigators, including Georgia Clinical and Translational Science Institute, electronic mailings, announcements on social media sites, fliers posted in the community, clinics and hospitals, and ResearchMatch.org recruitment tools. ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University. There is no cost for researchers at participating institutions in the ResearchMatch Network to use ResearchMatch for the purposes of feasibility analysis or recruitment. The Vanderbilt IRB provides oversight for ResearchMatch as a recruitment tool and this has been documented within the ResearchMatch IRB Letter of Understanding (available upon request). However, individual requests to use ResearchMatch as a recruitment tool should be submitted to the participating institutions' IRBs. We also will recruit from primary care practices affiliated with Emory Healthcare. We will aim to recruit a diverse sample that includes ≥25% males and ≥30% minorities. In our pilot work, 19.5% of the participants were men, while 42.7% were racial minorities. Our target sample for under-represented racial/ethnic minorities is attainable in Atlanta where the residents are 40.4% white, 49.8% black and 4.8% Asian.

Individuals who respond to recruitment solicitations will be directed to a web link that provides a brief overview of the study and eligibility criteria. Those who are eligible will be guided to click a link to complete a battery of 8 brief questionnaires which are outlined with their validation references in Table 1 (used in recent pilot studies). We transferred 7 of the questionnaires to the RedCap platform so they can be completed online in one or multiple sittings within 30 mins. Data from the questionnaires will be used for eligibility screening and to examine the impact of sleep disturbance, health status, stress, and risk of depression on study outcomes. The eligibility criteria are embedded within the online surveys so that the data collection is terminated when a potential participant enters information that makes them ineligible (e.g., history of stroke). Those who complete the RedCap questionnaires will be scheduled for a 15-min phone interview, during which the BRFSS Physical Activity Questionnaire will be used to review past month's PA patterns. Individuals with <150 min of MVPA/wk will be scheduled for a 15-min technology set-up phone call when they will also be scheduled for baseline assessment.

Based on our experiences, we do not anticipate significant difficulties recruiting women, but more proactive strategies will be needed to recruit men and persons from underrepresented racial and ethnic groups. To address the challenge of recruiting men who are generally hesitant to enroll in behavioral studies, we will leverage the relationships that Emory has with strategic community stakeholders and establishments where men frequent, such as barbershops and service stations (flyers to be submitted later via modification after initial

study approval). In our recent pilot RCT, we were not able to leverage these resources, partly due to COVID-19 restrictions, and the number of men enrolled in the study was low at 19.5%. Yet all the men enrolled in the study were retained and had improvements in physical activity and cardiovascular outcomes that were comparable to those observed in women. These data suggests that the biggest barrier is getting men interested in screening for the study. We will address this barrier by having flyers that are intentionally designed for men and posted in strategic locations where men can conveniently access them. These resources will enable us to recruit a sample with at least 25% male representation. While it would be ideal to have equal representation of men and women in the study, extant data show more involvement of women than men in behavioral interventions. Therefore, we have selected a recruitment target which is more realistic in our setting.

**Retention strategy.**

The remote nature of our intervention and a protocol that requires no in-person visits will help reduce the burden to participants and hence increase the probability of enrollment, protocol adherence and retention in the study. In our pilot studies, the absence of in-person study procedures facilitated greater enrollment of minorities and promoted adherence and retention. We plan to reimburse participants' partial costs for the internet to increase our study retention and adherence to protocol. Participants will also be compensated for attending the scheduled assessment sessions. We expect that these strategies will help increase the chances of retaining our sample and obtaining complete data. We employed these strategies in our pilot RCT where our retention was 96.3%.

## 16. Withdrawal of Participants

If a participant develops a condition that impairs their mobility and ability to exercise safely without supervision (e.g., stroke), the PI will review if the condition has an impact on the participant's ability to continue with the study. All the decisions will be made in consultation with the participant. All adverse events associated with the study procedures will be reported to the IRB.

If a participant withdraw his/her consent for the use and disclosure of their identifiable information for some of the study procedures, he/she will also be withdrawn, in general, from further participation in the research study. Any identifiable research information recorded for, or resulting from, their participation in this research study prior to the date that they formally withdraw their consent may continue to be used and disclosed by the investigators for the purposes of the study.

## 17. Risk to Participants

1) Risks related to physical activity

To mitigate the risk, access to PATH resources will be controlled to ensure that participants are only using resources with align with their physical activity prescription based on their fitness status. As detailed in the study protocol, the study team will educate the participants about the importance of building up their physical activity regimen gradually by starting low and progressing slowly. Participants without a carpet will be encouraged to procure a Non-slip exercise mat or wear appropriate footware to reduce the risk of slipping during the workouts.

The study team will actively monitor our subjects to ensure they are staying within the appropriate level of safe workouts. To mitigate disappointment associated with failure to meet the set goals, the study team will provide support to participants and ensure they are aware of their right to withdraw from the study at any time.

2) Risks related to blood testing
To mitigate the risk, the study team will walk each participants through the process to make the lancet fingerstick use as painless as possible. All the potential risks associated with this test will be discussed with participants and will be monitored by the study team.

3) Risk of wearing a physical activity tracker
To minimize the risk, we shall ask participants who report irritation to stop using the rubber bands. The study shall mail to them a non-rubber wrist band which is not associated with irritation.

4) Risk of collection of private health information, internet and text message use, and recording of phone calls.
To minimize this risk, we will keep all files in a locked cabinet or on a secured server and will label questionnaires with an ID number. The link between ID number and names/other personal information will be kept by the principal investigator in a secure location (password protected document on our secured server). Questionnaires completed on the online program will be protected using online data protection measures that are built into the RedCap program to prevent data from being released. In addition, access to the PATH website will be password protected and robust data security measures will be employed as detailed under electronic data security management. All the data will be stored on the secure Emory server. Access to the research data is limited to members of the research team who have a need to access such information.

The PATH website will be hosted on the Amazon Web Services (AWS) at Emory Cloud Platform which is compliant with the Health Information Portability and Accountability Act (HIPAA). The platform is designed to cover the entire infrastructure of a website, including all regions, all zones, all network paths and all points of presence. Data collected from the PATH website will be transferred to a secure server (MySQL) using a secure HTTP connection. Hosting the website on the AWS Cloud Platform ensures that we benefit from their security team's efforts in fixing software vulnerabilities almost as soon as they're discovered. All connections to the servers will be encrypted and our front-end servers will be HTTPS only.

## 18. Potential Benefits to Participants

Participants may learn more about practical things that may help them become more physically active. Those who will manage to increase their physical activity may experience some of the benefits associated with physical activity including reduced risk of diabetes and heart disease.

## 19. Compensation to Participants

Participants will receive $20 for completing the baseline and end of study assessments (total=$40). These reimbursements will be done via ClinCard after the completion of baseline and end of study assessments, respectively. Participants will also receive $60 as reimbursement, via ClinCard, for using their data plan to access the workouts available on our PATH website. A participant must complete at least 70% of their weekly goal to be eligible for this reimbursement. The reimbursement will be paid at the end of the study.

All compensation is taxable income to the participant regardless of the amount. Individuals who do not provide a social security number may still participate in the research, but the IRS requires that 26% of the payment be sent by the institution to the IRS for 'backup withholding;' thus they would only receive 74% of the expected payment.

### 20. Data Management and Confidentiality

All technologies to be used in this study, including AWS webhosting platform, PATH website, Twilio, SR Fax, Actigraph, Fitbit, and Withings apps were reviewed and approved by Emory University's Enterprise Information Security Team. Prior to opening the screening phase, the PI and project manager will review and update the RedCap data dictionary, code book, algorithms for calculating scores and indices, and set alerts for values that were recently piloted in our feasibility studies. The updated data collection infrastructure will be tested by the study team before it is deployed for data collection. Audits will be performed monthly to ensure accuracy of data. Except for select physical assessment measures conducted at the baseline and 6-month assessments, all self-reported data are entered electronically by the study participant using RedCap software and sent to the university server and deposited in the study database.

The physical measures (BP, waist circumference, weight) will be recorded by the collector in a RedCap data entry form in real time as the data is collected. PATH website analytics, weight, BP, and PA self-monitoring data will be automatically captured through web-analytics and API interface with Fitabase, CentrePoint, and Withings cloud. Overall, the data receipt or uploads will be ongoing, electronic, and stored on a server at Emory University where it will be secured and backed-up. If a participant becomes pregnant, or develops an exclusion condition, the individual will be informed that they are no longer eligible for study participation, and their data will be censored effective on the date they were informed of the pregnancy or exclusionary condition.

The data manager will perform a weekly query to determine if there are missing data, outliers, confirm data collection is being done within expected window and that there is logical consistency across the database. This report will be given to the PI for inclusion at weekly project meetings. Fitbit, CentrePoint, and Withings data will be reviewed during active participation so that outlier events can be determined if due to device error or participant over recording.

Confidentiality will be ensured by use of a simple identification number (ID), meaning it will not be encoded to denote other variables. Data will be stored on a password protected computer with access limited to the staff who monitor participants' adherence and safety, and the data management team. Any data that will be shared will need to be requested by use of a Data Request Form that requires specification of purpose of request, the variables, and dates/times of data collection, and intended dissemination. The request needs to be approved by

the PI, data set prepared by data manager, and oversight of analyses provided by the project statistician. An example of such a request includes doctoral students conducting secondary analyses for dissertation research.

Access to the master list of participant names and ID numbers will be limited to the staff who conduct the screening and intervention procedures as they need to interact with these individuals on a name basis. The staff who do not interact with participants after the assessments are blinded to name and treatment assignment.

If a participant declines to participate in all portions of the study, the participant will not be assigned a study ID number and the study coordinators/data collects will refrain from collecting any data on the participant. If the participant agrees to participate in some portions of the study by not others, the participant will be assigned a study ID number and the study coordinators/data collectors will be instructed to collect data only on those aspects of the study to which the participant has agreed to participate. These procedures will help prevent unauthorized inclusion of the patient's data in the database.

**Post-study data management**: The data collected from those who consent to continue using the PATH platform at the end of study will be managed using the same protocols employed in the study. The collected data will be limited to what is passively transmitted by their scale and tracker via API interface with our PATH platform.

Participants who consent to be contacted to participate in future studies will have their contact data securely stored in REDCap where it was originally collected as part of their sociodemographics. The permission for future contact will be limited to the PI and researchers at Emory University.

### 21. Plans to Monitor the Data to Ensure Safety of Participants and Data Integrity

A data safety and monitoring plan will be implemented to ensure the safety of all participants involved in the study and to ensure the validity and integrity of the collected data. The PI and biostatistician (Kariuki, Sereika) in conjunction with the project coordinators and staff, will be responsible for execution of this plan under the oversight of a safety officer and the IRB. Dr. Rebecca Gary, an expert in biobehavioral interventions, will act as the safety officer for this study. The PI will meet with the safety officer at least biannually (via Zoom or by teleconference) to evaluate the progress of the study including enrollment, assessments of data quality; timeliness of subject recruitment; accrual and retention; adherence to study protocol; any possible adverse events; external factors or relevant information and procedures designed to protect subject privacy and confidentiality. The safety officer will act in an advisory capacity to the PI and the National Heart, Lung, and Blood Institute (NHLBI) program director.

Each member of the study team will meet with the PI on a monthly basis and review confidentiality issues and complete a confidentiality agreement, prior to having contact with research subjects. Investigators and study personnel will meet monthly to discuss the study (e.g. study goals and modifications of those goals; subject recruitment and retention; progress in data coding and analysis; documentation, identification of adverse events or research subject complaints; violations of confidentiality) and address any issues or concerns at that time.

Minutes will be kept for these meetings and will be maintained in the study regulatory binder. The content of the data and safety monitoring report will include:

- Number of phone screen failures and reasons of failures
- Completion rates of each outcome measurement visit
- Protocol Deviations
- Randomization and participant characteristics
- Adverse Events (AEs), Serious Adverse Events (SAEs) and Unanticipated Problems
- Nature and severity of each event
- Participant complaints
- Study Modifications

A tracking system will monitor enrollment, track follow-up rates, and data entry processes, providing up-to-date status reports. A data entry system using RedCap will be constructed with data entry forms using checkboxes, drop-down menus, and branching logic to facilitate accurate data entry, routine data edit checks for consistency both within and between forms. All electronic files will be on a password protected server with regular backups. Personal information needed for tracking will be stored separately with limited access in locked file cabinets or under password protected files behind a firewall. Other measures directly obtained by equipment and online modalities (e.g., activity monitors or PATH website) will be merged with the database for analysis."

**What will be monitored and how frequently will the monitoring occur?**

Adverse events, assessment of changes to the risk/benefit ratio, acceptability of study continuation, breaches in confidentiality, and subject complaints will be reviewed by the principal investigator and reported to the IRB in accordance with IRB reporting guidelines. Any change in risk-to-benefit ratio will be provided to currently active subjects and once a modified consent form is approved by the IRB, active subjects will be re-consented if they decide to continue, and any new subjects will be consented with the new consent form. The PI (Dr. Kariuki) will be informed of SAEs as soon as they occur and will notify the NHLBI and safety officer within 24 hours of notification. The PI will then notify the IRB within 48 hours of the event. All other adverse events will be forwarded to IRB and within 7 days. Given the minimal risk nature of this study, we do not anticipate a large number of SAEs.

**Adverse and Serious Adverse Events**

For this study, an adverse event will be any reaction or undesirable event that occurs while a subject is on the research protocol whether or not it is considered related to any study interventions. Such events include illness, signs, symptoms, or clinically significant laboratory test abnormality that has appeared or worsened during the

course of the research study regardless of causal relationship to the study. Serious Adverse Event is an adverse event that results in one of the following:

1. Death – death due to any cause.
2. Life-threatening condition – the subject was at potential risk of dying at the time of the adverse event or it is suspected that the use or continued use of the study procedures would result in the subject's death.
3. Hospitalization – this indicates initial admission to the hospital or prolongation of a hospital stay that results from the adverse event.
4. Disability – the adverse event has resulted in a significant, persistent, or permanent change, impairment, damage or disruptions in the subject's body function/structure, physical activities, or quality of life.

Unanticipated adverse events are ones that are not previously reported or known to be associated with the study interventions. Generally, these are not mentioned in the consent form or final study protocol; however, should unanticipated adverse events which are possibly, probably or definitely related to the study procedures become common or serious, then the informed consent document will be modified accordingly.

What will be reported to the IRB?

The Investigators will submit the following data to the local IRB at the end of the study (this information may be submitted more frequently when necessary to ensure the safety of subjects in this study).

- The frequency of monitoring that took place during the course of the study.
- A summary of the cumulative adverse event data including a respective assessment of their relationship with study procedures.
- A summary of the assessment that was performed to evaluate external factors or relevant information that may have an impact on the safety of study participants or ethics of the research study.

A summary of the outcome of procedural reviews conducted to ensure subject privacy and research data confidentiality.

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

**Plan for sharing data**

It is our goal to make all data generated from this proposal available to other investigators without compromising the confidentiality of participants. The primary mechanism of data dissemination will be through submission of abstracts to regional, national, and international meetings and the submission of manuscripts. We may share de-identified data with other researchers or federal data repositories in the future. All requests for the de-identified data will be processed by the PI.

### 22. Provisions to Protect the Privacy Interest of Participants

Individuals names, addresses and sociodemographic data will be self-reported by participants on RedCap using the Sociodemographic questionnaire. The questionnaire will only be accessible to study staff and will be set up in a way that it can not be downloaded with identifiable information. Anthropometric and physiologic measures will also be documented by the study staff on. The informed consent documents collected via REDCap will not be downloaded but will be stored within the REDCap HIPAA compliant server. On the PATH website forum, particpants will make their contributions and engage with other participants using their study IDs instead of their names. There will be no provision for participants to private message each other and the forum will be monitored and moderated by the study staff to make sure that the conversations are civil and focused on the study aims.

### 23. Economic Burden to Participants

Participants may incur additional internet costs for using YouTube workout videos for exercise. We will reimburse these expenses at the end of the study. Participants are also compensated for their time in completing the assessments and questionnaires, they are also permitted to keep the scales, waist circumference tape measure, and Fitbit Charge 5, and exercise equipment.

### 24. Informed Consent

Written consent for study participation will be obtained via REDCap before or during the baseline assessment session conducted via zoom. The study staff conducting the assessment will discuss the procedures of the study to the participant and answer any questions and concerns they may have before signing the consent forms. An electronic copy of the informed consent form will be sent to each participant via email, while a signed copy will be retained in the investigator's study records.

Participants who would like to continue accessing the PATH platform at the end of the study will be asked to give verbal consent during their last coaching session or during their end of study assessment. The study staff will read to them the IRB approved script for the post-study consent and document their response on REDCap.

A waiver to document consent is requested for this study.

Non-English-Speaking Participants will not be included in this study because all our intervention materials are only available in English.

Participants who are not yet adults and cognitively impaired adults will not be included in this study.

### 25. Setting

We will conduct the study at Emory University and recruit participants primarily from the Atlanta metro region. To obtain our target sample (88) we will use resources available to Emory investigators, including Georgia Clinical and Translational Science Institute, ResearchMatch (free registry of research volunteers), electronic mailings, announcements on social media sites, and fliers posted in the community. We also will recruit from primary care practices affiliated with Emory Healthcare. We will aim to recruit a diverse sample that includes ≥25% males and ≥25% minorities.

### 26. Resources Available

We intend to recruit a diverse group of participants including ≥25% males and ≥25% minorities. Based on our pilot study, we expect to screen about 470 adults (including 87 minorities) to successfully enroll 88 individuals with 25% minority representation. We will use several strategies to conduct recruitment including leveraging resources available to Emory investigators, including Georgia Clinical and Translational Science Institute, ResearchMatch (free registry of research volunteers), electronic mailings, announcements on social media sites, and fliers posted in the community. We also will recruit from primary care practices affiliated with Emory Healthcare.

The proposed study timeline is 12 mos. During the first 3 mos, we will optimize the PATH platform using recent pilot data, finalize the study protocol, obtain Institutional Review Board and Data and Safety Monitoring Plan approval, and finalize the recruitment strategies. We will also hire and train study staff. Study recruitment will commence from month 4-9, with a target to recruit 15 participants each mo. Since a rolling recruitment strategy will be adopted, assessments will continue concurrently with recruitment. In months 10-12, we will focus on finishing end of study assessments, data analysis and dissemination.

**Research Facilities and Resources, Research Centers, and Research Institutes at Emory**

The facilities and other resources available at Emory University provide the collaborators of this proposal with a rich environment, supportive of successful scientific research involving environmental exposures and their impact on human health. Emory University's health sciences schools have faculty and staff who are well trained in human subjects research and the conduct of clinical and epidemiologic research and well equipped to conduct the proposed research; its clinical facilities provide settings for recruiting, enrolling, and following research subjects; and its laboratories provide access to specialized core facilities.

**Office of Nursing Research**

The over-riding mission of the Office of Nursing Research (ONR) is to facilitate faculty and students in the generation, dissemination, and application of knowledge as it relates to nursing care of individuals and families across the lifespan and around the globe. To this end, the Dean of the School of Nursing has invested significantly in the ONR. The ONR includes the Associate Dean for Research Operations (Drenna Waldrop, PhD); the Director of the Biostatistics and Data Management Core (Melinda Higgins, Ph.D); 3 FTE

Methodology/Statistical Experts; a Data Manager; a Biobehavioral Lab Director (Whitney Wharton, PhD); a Lab Manager; 1 Grant Editor; full-time Pre-Award Specialists; full-time Post-Award Specialists; a full-time Senior Research Program Coordinator; and a full-time Project Manager. Each of these individuals works to foster a climate of research facilitation and productivity.

Multiple resources are provided by the ONR. Briefly, as soon as a faculty member or student alerts the ONR that he or she intends to submit a proposal, an electronic notification is sent to the Associate Dean for Research, and the Senior Research Program Coordinator. The Pre-Award Specialist, the Grant Editor, and the Statistical Team follow-up with the individual to begin discussions around the budget, to provide early methodological consultation, and to schedule an in-house, Mock NIH Review. These personalized contacts remain active until the proposal is submitted. When a proposal is awarded, the Post-Award specialist assists the faculty member or student to manage the award effectively by preparing monthly reports and reviewing them in regularly scheduled in-person discussions,

In addition to assisting faculty in grant submissions and management, publishing resources and manuscript editorial support is also offered through the ONR. Monthly series of research roundtables and colloquia provides additional opportunities for interdisciplinary dialogue and collaboration. In addition, the statistical team holds regular statistical workshops each semester, well attended by students and faculty alike. To coordinate all interactions, the offices of the ONR team are grouped in a complex on the second floor of the Nursing School.

**Nell Hodgson Woodruff School of Nursing Biobehavioral Research Laboratory**

The Nell Hodgson Woodruff School of Nursing Biobehavioral Research Laboratory includes 400 sq. ft. of dedicated space that serves as a resource for use by School of Nursing and affiliated researchers. This laboratory is equipped for processing and analyzing samples and is outfitted with a Beckman-Coulter refrigerated centrifuge, a 4-degree refrigerator, one -20 and three -80 freezers for long-term storage of clinical samples. Additionally, the lab is equipped with a biotech plate reader, ultra-pure water maker, pipettes, blood drawing supplies, processing tubes and other equipment and supplies needed to advance the range of biobehavioral research conducted in the School of Nursing.

**Offices/Computing**. All faculty members in the School of Nursing have private offices with full computing capabilities networked to printers. Each research faculty has a separate research office space for housing research nurses and activities. The trainees are provided with access to the faculty's research office and have access to another designated, computer-equipped offices shared with other trainees. Conference rooms and medical media service are provided throughout the relevant buildings. Each office is equipped with desk space, telephone, computer, and file storage space as well as convenient access to photocopying, and conference rooms. Financial and administrative support is readily available and located in offices near the investigators. Through the Emory network faculty can use the Emory Integrated Computing Core (EICC) for analyses exceeding their desktop machines' capabilities. For more computing power, Emory faculty can now access the cloud computing resources of Amazon Web Services.

**Core Research Facilities**

The Core Research Facilities provides essential technical services required for scientific study. Services provided include specialized laboratories within the various schools of the health center, equipment and associated consultation. Specialized research facilities of particular importance include the Wayne Rollins Research Building, the Whitehead Biomedical Research Building, the Health Sciences Center Library, and The Emory Center for Outcomes Research, and the General Clinical Research Center (see clinical resources).

**Department of Mathematics and Computer Science**

Through the Department of Mathematics and Computer Science, we have access to the following resources:

- Two shared memory, multi-processor systems primarily suited for multi-threaded, CPU intensive programs. One is a Microway system, with 4 Intel Xeon E5-4627 CPUs with 40 cores and 1TB memory running Ubuntu Linux. The other is a Dell R510 system with 2 Intel Xeon X5670 CPUs with 12 cores and 128 GB of memory running CentOS Linux.
- A high performance cluster with 32 nodes and 128 processor cores. Each node has two dual core AMD 2214 2.2 GHz Opteron CPUs, 4 GB RAM and an 80 GB drive. The nodes are connected via a High Performance InfiniBand network and Gigabit Ethernet. The nodes are running Linux CentOS. A head node running Rocks manages the cluster and it is using the Portable Batch System to schedule jobs.
- A parallel computing cluster with 32 CPUs and 16 GB of memory split across 16 systems. All nodes use RedHat Linux/Intel for their operating system. Nodes are interconnected with switched, 100 Mb Ethernet. Two build environments are available for MPI programs. One uses the GNU compiler suite [gcc/g++/g77]; the other uses the Portland Group (PGI) compiler suite.
- Storage for departmental servers and workstations is provided by an 8 GB/sec Fiber Channel Storage Area Network. Currently there is 14TB of disk storage provided by Sun StorEdge T3B and 3511 raid arrays. The storage is further backed up daily on a set of additional raid disk devices and ultimately cloned to the QualStar 5244 SAIT tape robot.

These facilities are housed within the Mathematics and Computer Science Department, Emory University, and are maintained and managed by the department's four full time system administrators. Support in terms of network connectivity, software and hardware installation, maintenance, and trouble-shooting is provided by the university.

**Emory University Library and Information Technology Services.**

Emory University's division, Library and Information Technology Services (LITS), is Emory University's central Information Technology department, supporting all missions of research, healthcare, education, and administration. The Office consists of over 600 professional information technology employees and manages all technical infrastructure (networking, data centers, service centers, etc.), information security infrastructure, enterprise-wide applications, healthcare delivery systems, and enterprise research platforms.

**Research Electronic Data Capture (REDCap)**

REDCap is a secure, internally hosted web-based application designed specifically to support data capture for research studies. REDCap is an open source software program supported through a consortium led by Vanderbilt University. REDCap is a metadata driven electronic data capture system available for investigators to use for form-based data collection. The system is supported by Emory's Office of Information Technology (OIT) and hosted on an OIT virtual machine (VM) environment with nightly backup and full redundancy for high application availability and reliability. REDCap is a web-based system with the Apache/PHP web server located in the DMZ and the MySQL database backend hosted in a HIPAA compliant secure data zone. Access to the system requires an Emory University or Emory Healthcare user account with external users supported using Emory University sponsored accounts.

Key features and benefits of REDCap include:

- An intuitive interface for data entry (with data validation)
- Audit trails for tracking data manipulation and export procedures
- Automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R)
- Procedures for importing data from external sources
- Facilitates compliancy with Emory's HIPAA policies and procedures
- Advanced features, such as branching logic and calculated fields

More information available at: https://it.emory.edu/catalog/data-and-reporting/redcap.html

**Office of Information Technology**

Emory Office of Information Technology (OIT) is Emory University's central Information Technology department, supporting all missions of research, healthcare, education, and administration. OIT consists of professional information technology employees and manages all technical infrastructure (networking, data centers, service centers, etc.), information security infrastructure, enterprise-wide applications, healthcare delivery systems, and enterprise research platforms.

- **Research IT Environment:** Emory University operates a high-speed, research information technology infrastructure to support the research mission of the University. With a high speed ten gigabyte fiber as its backbone, the network provides speeds of up to a gigabyte to the desktop and ten gigabytes throughout the internal campus with several points of redundancy through to the commodity Internet and Internet 2. Physical servers and hardware are stored in a 24x7 monitored professional data center with environmental and physical controls in place. The University hosts virtual server farm and petabytes of storage that can quickly be provisioned based on investigator needs. From a security perspective, Emory University adopts a defense-in-depth strategy incorporating security and privacy controls at a policy, operating system, network device, and intrusion prevention systems. The University has HIPAA compliant network zones and infrastructure in place and implements encryption mechanisms to secure sensitive data at rest and in transit.

- **Research Data Systems and Applications:** Data systems and applications used for research purposes can be hosted and administered on Emory OIT servers, either physically or through Virtual Machine environments. Emory OIT implements best practices in application management and support, such as maintaining application, database and web interface components on separate servers, establishing backup / fail over server redundancy for service continuity and system and data recovery, and maintaining distinct development, test and production environments for efficient application testing, upgrade and deployment. Access to systems in the Emory network zone is supported by secure two-factor authentication VPN connection and remote access tools, and by state-of-the-art technology for identity management, authentication, and account credentials encryption. Role-based permission controls ensure that users have appropriate access to the designated functions and data records in applications and underlying databases, including row-level partitioning whenever deemed necessary. Emory OIT applies regular functionality and security software, hardware and operating system patching and upgrades, according to policies and program-specific service-level agreements. Research applications that make use of patient health information are not directly connected to the electronic medical record system. Instead, applications may draw on data extracted from the Emory clinical data warehouse read-only environment maintained by Emory Healthcare Information Systems, or on data abstracted from data instruments and entered in research applications and databases maintained by OIT, such as the Redcap data capture system, and program-specific data repositories.

**Research Facilities and Resources, Research Centers, and Research Institutes at Pitt**

Although no research activities will take place at the University of Pittsburgh, there co-investigators from the University will be involved in the project. The resources available to the co-investigators include:

**Computing Services and Systems Development (CSSD)**

CSSD provides the network infrastructure and telecommunications backbone for the University community. The proposed study will use this infrastructure to save time and costs. The University's data network, PittNet, connects thousands of computers at all five University campuses to the Internet. Ethernet connections are the standard for University offices. Off-campus students, faculty, and staff have access to PittNet through broadband and VPN access. Extensive telecommunications support is provided to more than 18,000 telephones as well as telegraph, voice mail, telephone credit cards, paging support, and large-group conference call service. The Technology Help Desk is available 24 hours a day, seven days per week. The Technology Help Desk provides troubleshooting, problem resolution, and answers "how to' questions on a variety of information technology issues. An online service, Knowledgebase, provides users with access to solutions and recommendations from the Technology Help Desk.

**School of Nursing Center for Research and Evaluation (CRE)**

The CRE of the School of Nursing houses a data lab for use by research staff and doctoral students that contains 8 Dell desktop computers (Intel Core i7 processor with a minimum 16MB RAM) running either Windows 7 Ultimate or 10; a black and white HP LaserJet Printer, a Dell laser color printer, and 2 flatbed scanners (with document feeders). Two additional Fujitsu scanners are dedicated to support data entry via optical scanning via Teleform. In addition to Microsoft Office 2013 (Word, PowerPoint, Excel, Access), the lab contains the full- versions of the major statistical software packages (SAS 9.4, SPSS 22, STATA 13.1, R). Specialty statistical packages are also accessible in the data lab, including Mplus 7.31, LISREL 9.2, EQS 6.1, and AMOS 22.0 for structural equation

modeling; HLM 7.01 for hierarchical linear modeling; CMA 3.0 for systematic reviews and meta- analyses; StatXact 11.0 and LogXact 11.0 for discrete data.

### Trial Management Plan

**Overview.** Successful trial management requires recognizing that risks are an integral part of a trial and therefore risk management is critical and includes being able to identify potential risks throughout the trial by a series of steps: assess, plan, track, and prevent or mitigate. This is dependent on having knowledgeable, competent leadership that will implement a systematic process for identifying and evaluating events that could impact the quality, safety, timeline, and budget related to achieving the objectives of the trial.

**Governance**. Figure 1 depicts the governance structure of the proposed trial, with the components in blue representing the Investigative Team (IT), green representing consultant and those in gold the research staff. Here we describe the trial's governance and how a systematic process of risk identification and management will be implemented. The PI (Kariuki) will oversee the project management with daily oversight of operations and weekly meetings to review and discuss progress, timelines and potential problems. The PI will monitor budget and fiscal status in consultation with the Grants Administrator overseeing the project, set and reinforce study timelines, monitor study progress, finalize IRB protocol modifications, and communicate with the IRB, safety officer, and NHLBI Program Officer. The PI will develop agendas for the weekly Project Meeting and Quarterly Investigators Meeting, which will be held in person or videoconferencing. The agenda, and several reports, e.g., Timeline Progress Report, Participant Flow Figure, Assessment Adherence Table, and Assessment Completion Table, will be sent prior to the weekly Project Meeting. The PI will review the meeting minutes, which will be stored in a central depository (e.g., OneDrive).

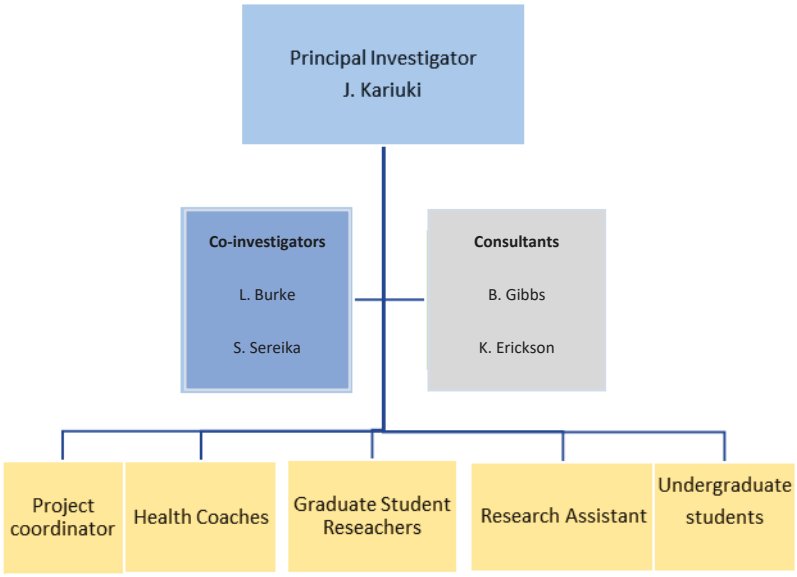


Figure 1. Governance Structure of the Proposed Project

The IT comprised of the PI and Co-Is will be the major decision-making unit for overall scientific direction, including final decisions

| Table 1: Goals of the Trial Management Team |
|---|
| • Develop governance standards that promote accountability |
| • Facilitate safe, quick recruitment of target sample |
| • Track progress to aims and use of resources |
| • Assess success of existing processes and status of study |
| • Identify, assess, plan, track and control risks, issues, or other concerns. |
| • Use problem-solving strategies to focus on problem analysis (e.g., root cause analysis) collaborative decision-making, and execution with work plans. |
| • Report pertinent issues and data to NHLBI, IRB, DSMO |
| • Ensure timely achievement of milestones/ study completion |
| • Disseminate findings, share data as indicated |

regarding study assessments, measurements, interventions, and other research procedures. At the quarterly IT meeting, the group will review recruitment, screening, and assessment of potential participants, and adjudicate final inclusion/exclusion decisions; if necessary, a meeting will be called at shorter intervals. This group will also be responsible for resolving any disputes on scientific issues, e.g., publications or authorship.

**Role of Project Manager.** The administrative duties will include being responsible for the daily oversight of: (1) development and maintenance of standard operation procedures; (2) training and supervising research staff and students; (3) monitoring participant recruitment, retention and randomization and developing participant flow chart reports for the weekly project meetings; (4) maintaining records for the quarterly recruitment and annual NIH progress reports. She will be assisted by the Research Coordinator in developing and maintaining updates to the Manual of Operations and submitting protocol modifications to the IRB. The Project Manager is a masters prepared health care professional who has extensive research and clinical trial experience, including intervention delivery, working with mobile health devices, overseeing recruitment and randomization, and monitoring data management, participant engagement and retention. The Project Manager will work closely with the Research Coordinator. For our proposed study, the Research Coordinator will be responsible for: (1) coordinating recruitment, screening, and conducting remote assessments; (2) training additional staff to assist with these study procedures; and (3) preparing submissions to the IRB and quarterly recruitment reports to the NIH. Critical features in a RCT that need to be managed on a daily to weekly basis include ensuring safety of the study participants by reducing any potential risks of participation, screening interested individuals to ensure they can safely participate and complete the trial, facilitating a consistent flow of eligible participants for randomization, promoting adherence to the study protocol and retention in the trial to ensure adequacy of sample for data analyses, monitoring intervention delivery to ensure treatment fidelity, and overseeing data collection and data management to ensure accuracy, confidentiality, and blinding of data collectors.

### 27. Multi-Site Research When Emory is the Lead Site

All research activities will happen at Emory and Atlanta metro area. The study collaborators from other institutions will support the study as follows:

**Co-Investigator:** Lora E. Burke, PhD, MPH, FAHA, FAAN, is a Professor in the Department of Health and Community Systems in the School of Nursing at the University of Pittsburgh, with secondary appointments in the Department of Epidemiology in the Graduate School of Public Health and in the Clinical Translational Science Institute. Dr. Burke has been a primary mentor for the PI and has worked with him in all stages of developing and pilot testing the intervention that will be tested for efficacy in this proposal. She will advise the PI on clinical trial administration and guide the study team on strategies to enhance protocol adherence and study retention.

**Co-Investigator:** Britney Beatrice, MS, is an instructor of dietetics at the University of Pittsburgh's School of Health and Rehabilitation Sciences. She has extensive experience as a lead interventionist in several large scale RCTs, including the recently completed SMARTER study (PI Burke) where she worked closely with Dr. Kariuki on his diversity supplement on the study. At baseline and 6 months, she will guide the study team in the collection of dietary recall data. In addition, she will guide the measurement of the diet quality using the Healthy Eating Index (HEI) and enter the data on RedCap. She will also use the standard behavioral treatment (SBT) resources developed by co-I Burke, to curate the materials needed to address components of healthy diet that are described in grant. Each month, both the intervention and control group participants will receive a brief PDF addressing one of the diet components. She will be responsible for ensuring that the curated content focuses on improving diet quality to reduce CVD risk and improve general health.

**Co-Investigator:** Susan M. Sereika, PhD, is a Professor in the School of Nursing with secondary appointments in the Departments of Biostatistics and Epidemiology in the Graduate School of Public Health, and in Clinical Translational Science Institute at the University of Pittsburgh. Dr. Sereika has worked closely with the PI in the preparation of the analysis section of the submitted proposal. She will provide oversight to treatment randomization, chair data meeting, supervise all statistical work, analyze the adherence and cardiovascular outcomes data for Aims 3 and 4. She will also assist in the preparation of reports (including safety) and collaborate in dissemination of research findings from this study.

**Consultant:** Bethany B. Gibbs, PhD, is an Associate Professor and chair of the Department of Epidemiology and Biostatistics at West Virginia University School of Public Health. She is trained in cardiovascular and physical activity epidemiology. Her background in lifestyle changes trials, kinesiology and physical activity data analysis. Dr. Gibbs has provided valuable input in all stages of developing the PATH intervention, especially in the integration of the coaching component with other components of the intervention. Dr. Gibbs will advise on PA monitoring and coaching strategies including training and quality assurance.

**Consultant:** Kirk Erickson, PhD is the Director of Translational Neuroscience at AdventHealth Research Institute. He has extensive experience in exercise physiology, exercise training, and clinical trial design and implementation. He was a member of the 2018 Physical Activity Guidelines Advisory Committee and authored the 2020 American College of Sports Medicine Guidelines chapter on exercise prescription for Alzheimer's disease. He has worked closely with the PI and members of this team in several projects including recent work developing and pilot testing the PATH intervention. He will advise on recruitment, retention, physical activity prescription and analysis of data exploring the mechanisms of action driving any changes in physical activity.

**Consultant:** David Ogutu, BS, is the CEO and founder of Ritiko, a start-up that offers HIPAA compliant software solutions for Medicaid programs. Mr. Ogutu has a BS in Computer Science and Civil Engineering from MIT. Mr. Ogutu has closely worked with the PI in programming the PATH website, developing the PATH Fresher algorithm

and pilot testing the technological readiness of the platform. He will avail his technical know-how and Ritiko LLC resources to support the study through: 1) improving the capabilities and functionality of the PATH platform using the data collected in the pilot studies (e.g., optimize the mobile version of the platform as suggested by participants; 2) Optimize the PATH Fresher algorithm to make it more effective in identifying new workouts that are likely to appeal to our target population; 3) interfacing the PATH website with near real-time Fitbit data via Application Programming Interface to Fitabase and writing a script that prompts automatic fetching of the physical activity and last sync data on an hourly basis throughout the study period (in the SMARTER trial we learned that this could help reduce the amount of missing data over a 12 month period), 4) Program a PATH platform ecosystem that will send automated physical activity reminders (emails and text messages) based on each participant's preferred schedule, 5) setting-up web-analytics to enable real-time participant monitoring on the use of the PATH website, and 6) programming automated weekly summaries of PATH utilization analysis for the study team. During the entire duration of the study, he and Ritiko staff will troubleshoot and address any technical problems that may emerge. They will also offer regular services related to maintaining the site and data backup and will be responsible for maintaining the security and operations of the back-end server.

**Head Coach:** Heather Milton, MS is a board-certified clinical exercise physiologist, Certified Strength and Conditioning Specialist (CSCS®), and Certified Cancer Exercise Trainer (CET). She works as the Exercise Physiologist Supervisor at NYU Langone Health. She has extensive experience with remote coaching and has worked closed with the study team to develop and pilot thest the intervention. She will be the lead coach and will train and supervise the coaches who will be working directly with participants.

**Coach:** La'Vette Wagner, BS is a certified health coach. She will be on the standby to support current study coaches incase of unforeseen circumstances that may limit their availability.

**Clinical Research Coordinator:** Redet Kebebe is a registered nurse also trained in clinical research. She will be on the standby to support current study coordinator incase of unforeseen circumstances that may limit her availability.

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## 29. Protocol Checklist

**Please note that protocol sections with an asterisk (*) should always be included in the protocol; if the section does not have an asterisk, and you have not included the section in the protocol, the IRB will consider it your attestation that the section does not apply to your study.**

| **Protocol Section** | **Added to the protocol?** |
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| **External Collaborators**- if applicable, add each external collaborator information and indicate whether that institution's IRB will review (or has already reviewed) that individual's engagement in human participants research activities) | ☒ **Yes** |

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| **Funding Source***: Include the information for the funding entity for this study. Please explain if this study is covered by a sub-award or other pertinent information. Say "department" if you do not have any other funding. | ☒ **Yes** |
| **Objectives*:** Describe the purpose, specific aims, or objectives and state the hypotheses to be tested | ☒ **Yes** |
| **Background*:** Describe the relevant prior experience and gaps in current knowledge. Describe any relevant preliminary data. Provide the scientific or scholarly background for, the rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge | ☒ **Yes** |
| **Study Endpoints*:** Describe the primary and secondary study endpoints. Describe any primary or secondary safety endpoints. | ☒ **Yes** |
| **Study Intervention/Investigational Agent*:** Describe the study intervention and/or investigational agent (e.g., drug, device) that is being evaluated. | ☒ **Yes** |
| **Drug/Device Handling:** If the research involves drugs or devices, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on participants and be used only by authorized investigators.<br>If using a drug, explain if the control of the drug is managed by IDS (or VA/Grady/CHOA research pharmacies). If not, provide IDS exemption document.<br>If a device, explain how the device is being stored and managed. | ☐ **Yes** |
| If the drug is under an FDA REMS, plan to complete the REMS checklist found here, on the IRB website. | ☐ **Yes** |
| If the drug is considered a controlled substance, make sure you have filled out this form. | ☐ **Yes** |
| If applicable, identify the holder of the IND/IDE/Abbreviated IDE. An Emory investigator who holds an IND or IDE is considered to be a Sponsor-Investigator (S-I). If the study is under an S-I, review this section of our website for additional requirements. | ☐ **Yes** |
| **Procedures involved***: Describe and explain the study design and include a study schema. Describe all research procedures being performed and when they are performed, including procedures being performed to monitor participants for safety or minimize risks | ☒ **Yes** |
| **Procedures-Minimizing risk*:** describe the procedures performed to lessen the probability or magnitude of risks. | ☒ **Yes** |
| **Procedures- Drug/Device Use:** describe all drugs and devices used in the research and the purpose of their use and their regulatory approval status | ☐ **Yes** |
| **Procedures-Source Records*:** describe source records that will be used to collect data about participants. Attach all surveys, scripts, and data collection forms to the submission. | ☒ **Yes** |

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| **Procedures-Data collection*:** describe what data will be collected during the study and how that data will be obtained | ☒ **Yes** |
| **Procedures- Long Term Follow Up*:** once all research-related procedures are complete, what data will be collected during this period. If no data is collected after procedures are completed, please state in the submission. | ☒ **Yes** |
| **Data and Specimen Banking:** describe where the specimens will be stored, how long they will be stored, how the specimens will be accessed, and who will have access to the specimens. Depending on the volume and nature of the collection, this may require a separate repository-specific IRB submission. The VA Data Repository SOP is required if the study is creating a data repository at the Atlanta VA.<br>List the data to be stored or associated with each specimen.<br>Describe the procedures to release data or specimens, including the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens. | ☒ **Yes** |
| **Sharing of Results with Participants*:** Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with participants or others (e.g., the participant's primary care physicians) and if so, describe how the results will be shared If applicable (e.g. for studies involving scans and/or panels of exploratory testing on specimens)<br>Plan for managing the types of findings that might arise. This should include any secondary findings that are being sought actively, findings that might be anticipatable, and findings that might be un-anticipatable.<br>Plan for recognizing, analyzing, and handling incidental findings and how incidental findings will be communicated to participants during the consent process. If the plan is not to disclose any findings, then this should be included. This plan might include the option for participants to opt-out of receiving incidental findings.<br>Description of the research team's responsibilities following disclosure of a finding. This should detail educational information about the nature of the finding, how to seek care from a clinician or specialist, obtaining health insurance to secure treatment, and/or referral to a clinical specialist, if one is required.<br>Reminder to include language in the consent form to let the participants know your plans for this – see Modular Language for Informed Consent Forms on IRB website) | ☒ **Yes** |
| **Study timelines*:** describe the duration of an individual participant's participation in the study; anticipated time to enroll all study participants and the estimated date for the investigators to complete this study (complete primary analyses) | ☒ **Yes** |

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| **Inclusion and Exclusion Criteria*:** describe how individuals will be screened for eligibility and the criteria that define who will be included or excluded in your final study sample | ☒ **Yes** |
| **Population*:** describe the study popualation and indicate specifically whether you will include or exclude each of the following special populations:<br>• Adults unable to consent<br>• Individuals who are not yet adults (infants, children, teenagers)<br>• Pregnant women<br>• Prisoners<br>Note: you cannot exclude people with limited English proficiency unless you can demonstrate the scientific need for such exclusion.<br>Community Participation: For studies aimed at addressing issues that affect a certain community or group: How, if at all, will this study involve people from the target community in the design of the study? Conduct of the study? How will the results of the research be shared with the participants and/or the target community/ies?<br><br>**If studying Race or Ethnicity, have you defined these terms, and explained their proposed mechanism of action if these characteristics will be used in an explanatory model?** | ☒ **Yes** |
| **Research with pregnant women, fetuses, or neonates:** review this checklist to verify you have provided enough information to ensure the safety and well-being of this population. | ☒ **Yes** |
| **Research with neonates of uncertain viability:** review this checklist to verify you have provided enough information to ensure the safety and well-being of this population. | ☒ **Yes** |
| **Research involving prisoners:** review this checklist to verify you have provided enough information to ensure the safety and well-being of this population. | ☒ **Yes** |
| **Research involving children:** review this checklist to verify you have provided enough information to ensure the safety and well-being of this population. | ☒ **Yes** |
| **Research involving cognitively impaired adults:** review this checklist to verify you have provided enough information to ensure the safety and well-being of this population. | ☒ **Yes** |
| **Research involving economically or educationally disadvantaged persons:** describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects | ☒ **Yes** |
| **Local Number of Participants*:** Indicate the total number of participants to be accrued locally. If applicable, distinguish between the number of participants who are expected to be enrolled and screened, and the number of participants needed to complete the research procedures (i.e., numbers of participants excluding screen failures.) | ☒ **Yes** |

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| Provide your projected enrolling goals, including the percentage of participants according to sex and race. | |
| **Recruitment Methods*:** Describe when, where, and how potential participants will be recruited. Describe the source of participants. Describe the methods that will be used to identify potential participants. Describe materials that will be used to recruit participants. Attach copies of these documents with the application.<br>If including advertisements, attach the final copy of them. When advertisements are taped for broadcast*, attach the final* audio/videotape. You may submit the wording of the advertisement before taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/videotape. Describe the amount and timing of any payments to participants. Reimbursement for expenses/travel?<br>If using contests or raffles as incentive, you must offer entry to all potential participants, not just those who enroll in the study/complete study-related procedures, per Georgia State Law.<br>All research recruitment through social media needs to follow this guidance, which does not allow the use of personal social media accounts for some recruitment activities. | ☒ **Yes** |
| **Withdrawal of Participants*:** Describe anticipated circumstances under which participants will be withdrawn from the research without their consent. Describe any procedures for orderly termination. Describe procedures that will be followed when participants withdraw from the research, including partial withdrawal from procedures with continued data collection. | ☒ **Yes** |
| **Risk to Participants*:** List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the participants related to the participant's participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.<br>If applicable, indicate which procedures may have risks to the participants that are currently unforeseeable.<br>If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.<br>If applicable, describe risks to others who are not participants. | ☒ **Yes** |
| **Potential Benefits to Participants*:** Describe the potential benefits that individual participants may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit. Do not include benefits to society or others. | ☒ **Yes** |

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| **Compensation to Participants*:** Describe if/how subjects will be compensated for participation in this study. Indicate what method compensation will be delivered (e.g. cash, gift card, school credit). Describe the amount and timing of any payments to participants. How much? What kind? Is tax information required? (if so, must be reflected in the informed consent form). Will payments be pro-rated if a participant withdraws early? | ☒ **Yes** |
| **Data Management and Confidentiality*:** Describe the data analysis plan, including any statistical procedures or power analysis. Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission. Describe any procedures that will be used for the quality control of collected data. | ☒ **Yes** |
| **Describe how data or specimens will be handled study-wide*:** What information will be included in that data or associated with the specimens?<br>• Where and how data or specimens will be stored?<br>• How long the data or specimens will be stored?<br>• Who will have access to the data or specimens?<br>• Who is responsible for receipt or transmission of the data or specimens?<br>• How data or specimens will be transported? | ☒ **Yes** |
| **Data Monitoring and Participants Safety (if this study is more than minimal risk, this section is required):**<br>Ensure that you review our Data and Safety Monitoring plan guidance for specific details about this section, and examples of what the IRB will be requiring according to the level of risk.<br><br>If a DSMB is needed, please describe the composition of the board (if not already detailed in the protocol). Review this guidance for more information. If the sponsor protocol does not contain all required information, please in this section.<br><br>Describe the plan to periodically monitor the data at the site level according to risk level. Include the appropriate completed monitoring table, if applicable.<br><br>Description of the plan for notifying the IRB of reportable events, whether the sponsor requires reporting above and beyond the Emory IRB reporting requirements, and if so, a description of the requirements and plan for meeting them.<br><br>Please address the specific details below. If deemed not applicable, please provide rationale: | ☒ **Yes** |

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| Subject safety:<br><br>• Specific subject safety parameters<br>• Frequency of subject safety observations<br>• Individual responsible for safety monitoring<br>• Subject stopping rules – under what conditions will a subject be removed from study participation and who will make the decision?<br>• Study stopping rules - under what conditions will the study be modified or stopped and who will make the decision?<br>• Reporting mechanisms (i.e. Deviations, adverse events, UPs)<br><br>Data Integrity:<br><br>• Specific data elements to be reviewed<br>• Frequency of monitoring data, points in time, or after a specific number of participants<br>• Individual responsible for data monitoring<br><br><u>Additional considerations for FDA regulated trials</u><br><br>Depending on the procedures affecting risks to participants, the site monitoring plan should specify:<br><br>• Categorization of activities done centrally and those on-site if applicable<br>• Monitoring methods (may include centralized/remote, on-site, and self-monitoring)<br>• Reference to any tools used (i.e. checklists)<br>• Identification of events that may trigger changes<br>• Identification of deviations or failures that would be critical to study integrity | |
| **Provisions to Protect the Privacy Interests of Participants*:**<br><br>• Describe the steps that will be taken to protect participants' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact with or whom they provide personal information.<br><br>• Describe what steps you will take to make the participants feel at ease with the research situation in terms of the questions being asked and the procedures being | ☒ **Yes** |

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| performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a participant might experience in response to questions, examinations, and procedures.<br>• Indicate how the research team is permitted to access any sources of information about the participants. | |
| **Economic Burden to Participants*:** Describe any costs that participants may be responsible for because of participation in the research. | ☒ **Yes** |
| **Consent Process*:** Describe where the consent process will take place, any waiting period available between informing the prospective subject and obtaining the consent; and the process to ensure ongoing consent.<br>Describe the role of the individuals listed in the application as being involved in the consent process; the time that will be devoted to the consent discussion; steps that will be taken to minimize the possibility of coercion or undue influence; and steps that will be taken to ensure the participants' understanding.<br>**Note**: If you are planning to obtain consent via electronic signature, please review this document. Additional guidance on consent documentation and process can be found on our website, under the consent toolkit. | ☒ **Yes** |
| **Consent Process-Non-English-Speaking Participants*:**<br>Indicate what language(s) other than English are understood by prospective participants or representatives.<br>If participants who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those participants will be in that language.<br>Indicate the language that will be used by those obtaining consent.<br>If you checked N/A, please provide reasoning of why subjects with limited English proficiency are excluded.<br>**Note**: if you stated that subjects with LEP will be enrolled, you are approved for the use of the Emory IRB short forms. Please read the guidance about the use of short forms here. | ☐ **Yes** |
| **Consent Process-Children:** After determining if the subject is a child per GA law (or if enrolled outside GA, per state/country law), please describe whether parental permission will be obtained from:<br>• Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the custody of the child.<br>• One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child. | ☐ **Yes** |

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| Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's general medical care.<br>When assent of children is obtained describe whether and how it will be documented per Emory Policies and Procedures | |
| **Consent Process-Cognitively Impaired Adults:** describe the process to determine whether an individual is capable of consent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require children to sign assent documents. | ☐ **Yes** |
| **Consent Process-Adults Unable to Consent:** List the individuals from whom permission will be obtained in the order of priority. (E.g., durable power of attorney for health care, a court-appointed guardian for health care decisions, spouse, and adult child.)<br>For research conducted in the state, review "46 LEGALLY AUTHORIZED REPRESENTATIVES AND SURROGATE CONSENT" to be aware of which individuals in the state meet the definition of "legally authorized representative."<br>For research conducted outside of the state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research.<br>Describe the process for the assent of the participants. Indicate whether:<br>• Assent will be required of all, some, or none of the participants. If some, indicated, which participants will be required to assent and which will not.<br>• If assent will not be obtained from some or all participants, an explanation of why not.<br>Describe whether the assent of the participants will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require participants to sign assent documents | ☐ **Yes** |
| **Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)**<br>Review the Emory IRB waiver document to ensure you have provided sufficient information for the IRB to make these determinations.<br>If the research involves a waiver of the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. | ☐ **Yes** |
| **Setting*:** Describe the sites or locations where your research team will conduct the research including where the subject will be identified and recruited, where the research procedures | ☒ **Yes** |

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| will be performed, and if you will involve a community advisory board. For research conducted outside the organization and its affiliates describe the site-specific regulations or customs affecting the research outside the organization and the local scientific and ethical review structure outside the organization. | |
| **Resources Available*:** Describe the resources available to conduct the research such us the feasibility of recruiting the required number of suitable participants within the agreed recruitment period; describe the time that you will devote to conducting and completing the research; describe the availability of medical or psychological resources that participants might need as a result of an anticipated consequences of the human research; describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions. | ☒ **Yes** |
| **Multi-Site Research when Emory is the Lead Site:**<br>Study -Wide Number of Participants: indicate the total number of participants to be accrued across all sites.<br>Study-Wide Recruitment Methods: If this is a multicenter study and participants will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods.<br>Describe when, where, and how potential participants will be recruited.<br>Describe the methods that will be used to identify potential participants.<br>Describe materials that will be used to recruit participants.<br>Describe the processes to ensure communication among sites. See "WORKSHEET: Communication and Responsibilities (HRP-830)." All sites have the most current version of the protocol, consent document, and HIPAA authorization.<br>All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record).<br>All modifications have been communicated to sites and approved (including approval by the site's IRB of record) before the modification is implemented.<br>All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies.<br>All local site investigators conduct the study in accordance with applicable federal regulations and local laws.<br>All non-compliance with the study protocol or applicable requirements will reported in accordance with local policy<br>Describe the method for communicating to engaged participating sites (see "WORKSHEET: Communication and Responsibilities (HRP-830)"):<br>• Problems (inclusive of reportable events). | ☐ **Yes** |

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| • Interim results.<br>• The closure of a study<br>If this is a multicenter study where you are a participating site/investigator, describe the local procedures for maintenance of confidentiality. (See "WORKSHEET: Communication and Responsibilities (HRP-830).")<br>• Where and how data or specimens will be stored locally?<br>• How long the data or specimens will be stored locally?<br>• Who will have access to the data or specimens locally?<br>• Who is responsible for receipt or transmission of the data or specimens locally?<br>• How data and specimens will be transported locally? | |