Official Title: A feasibility study of a step-goal based physical activity intervention in people with epilepsy

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Background, Rationale and Context

Epilepsy affects over 3 million people in the United States and over 65 million people worldwide.[1] One third of people with epilepsy (PWE) continue to have disabling seizures despite treatment with anti-seizure medications.[2] Even worse, currently available treatments often result in side effects that worsen epilepsy-associated comorbidities – including mood disorders[3] and cardiovascular disease.[4-6] These comorbidities are undertreated and significantly worsen quality of life (QOL) and health outcomes, complicate epilepsy management, increase health care costs, contribute to unemployment, and shorten the lifespan.[7-9]

Up to 80% of PWE exhibit cardiovascular comorbidities, increasing the risk of sudden cardiac death by threefold.[6] The "epileptic heart" is characterized in part by altered autonomic tone, resulting in increased rates of arrhythmia, myocardial infarction, and premature death.[10] A standard marker of autonomic tone is heart rate variability (HRV), which has consistently shown dysfunction and sympathetic dominance in PWE.[11] This is associated with increased mortality and sudden unexpected death in epilepsy.[12, 13] Exercise can improve HRV in other populations but has not been studied in PWE. Moreover, acute changes in HRV are associated with seizure occurrence[14] suggesting that altering HRV in PWE via exercise could translate to reduced seizure tendency. We plan to evaluate the potential of HRV as a biomarker in our future studies.

THE PROMISE OF PHYSICAL ACTIVITY

Animal studies show that physical activity (PA) can reduce seizure frequency across several models of epilepsy.[15-18] While small preliminary studies in humans have shown promising effects on seizure control,[19, 20] these effects have not been studied in large randomized clinical trials.[21] In other populations, PA has been shown to improve mood, cardiovascular health, and quality of life.[22-27] In some small prospective studies, PA interventions in PWE have shown improvement in depression, mood state, and QOL[28, 29] Thus, physical activity interventions have the potential to improve epilepsy across all dimensions of the disease, by improving seizure control *and* improving, instead of worsening, common epilepsy-associated comorbidities.

BARRIERS TO EXERCISE AND SEDENTARY BEHAVIOR IN PWE

There is **a need for a paradigm shift to improve PA in PWE**. Though PWE report that PA makes them feel physically healthy and happier, relieves stress and increases social interaction, they are still significantly less likely than the general population to follow physical activity guidelines.[30, 31] This may be due to a number of factors including lack of transportation, cognitive impairment, fear of having a seizure during exercise, medication effects, and stigma.[32, 33] A common worry among patients (and some providers) is that PA may trigger seizures, an outdated theory that has been disproven. In fact, current epilepsy guidelines reflect the importance of, and encourages, PA in this population.[34] Our and others' work have shown that exercise is safe in PWE,[20, 35, 36] but that neurologists rarely discuss PA with their epilepsy patients.[32, 33, 37]

RIGOR OF THE PRIOR RESEARCH

Previous small studies of exercise in PWE were not theory-driven and did not consider the unique barriers in this population, and as such were not sustainable.[20, 29, 36] In a prospective outpatient study, 15 women with drug resistant epilepsy underwent in-person guided aerobic exercise for 15 weeks, and showed a significant decrease in seizure frequency compared to baseline (mean seizures/week decreased from 2.9 to 1.7, a 40% reduction), but there was no control group for comparison.[20] Unfortunately, the intervention could not be sustained after the study ended, reducing the generalizability and implementation of such an intervention. Additional small (n ~20) randomized, controlled studies of exercise in PWE have demonstrated safety, improvement in QOL, mood, and cognition, but none have been shown sustainable behavior change in PWE, and have never investigated pathophysiological

mechanisms.[29, 38, 39] While small studies have shown that PA may be able to improve seizure control, mood, and QOL, larger trials for definitive efficacy are needed.[21]

SUPPORT FOR A STEP-GOAL BASED PA INTERVENTION

Steps are easily quantified by inexpensive monitors and are an easy metric to comprehend, which is particularly important given the cognitive limitations in PWE. Walking is the most preferred form of PA in PWE, can be undertaken in most locations without expensive equipment, and be achieved flexibly throughout the day (e.g., in a single sustained bout or several shorter bouts). Therefore, a walking intervention with an explicit volumetric target is the most likely to lead to long-term behavior change as individuals develop repertoires of personally-enjoyable walking activities (intrinsic motivation being a key driver of long-term behavior) that can be achieved during exercise, transport, sport, occupational ambulation, or home care. Most importantly, people learn to be active in the contexts in which they live and as such removal of the intervention does not mean removal of all of the supports they received during the intervention.

Consistent data support the use of a 7,000-8,000 step per day goal to achieve current recommendations for moderate-to-vigorous-intensity PA.[40] In numerous studies, self-selected PA intensity approximates or exceeds the minimum range recommended by the American College of Sports Medicine (ACSM).[41] In contrast, prescribed exercise intensities often result in feelings of displeasure and loss of autonomy, which interfere with the tenets of self-determination theory, thereby limiting uptake and sustainability.[42, 43] Thus, a step-goal based intervention with self-selected intensity is designed to address the unique barriers of this population, avoid undue stress (a common seizure trigger), and encourage uptake and sustainability. Our work and that of others has shown feasibility of remote interventions and wearables in PWE.[28, 44]

Objectives

Aim 1: To assess feasibility (adherence and sustainability) of a telehealth delivered, step-goal based PA intervention as measured by average daily steps achieved compared to steps assigned during the final 4 weeks of the intervention period (adherence) and the final 4 weeks of the maintenance period post-intervention (sustainability).

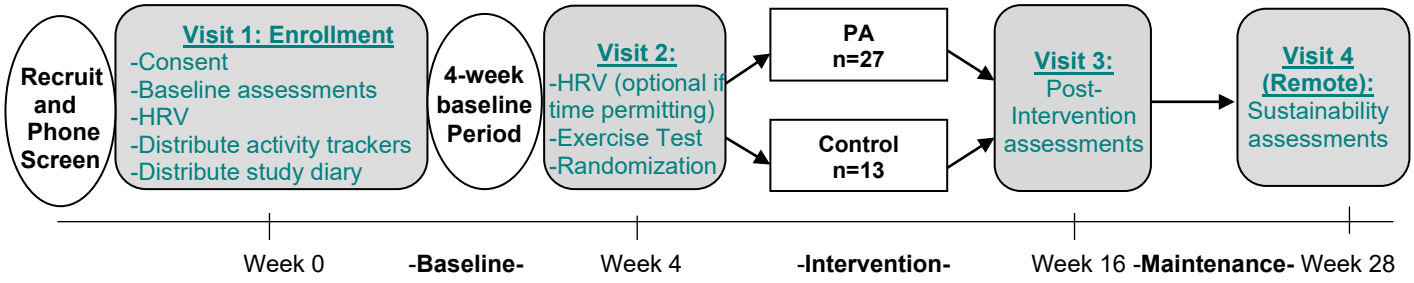
Aim 2: To assess the self-selected intensity distribution of activity in the intervention arm (time spent in objectively-assessed sedentary behavior, light-intensity, or moderate to vigorous intensity activity) to determine if they achieve intensities within the American Heart Association (AHA) guidelines.

Exploratory Aim 3: To explore estimates of variability of the effect size of a telehealth delivered, step-goal based PA intervention on seizures (measured by frequency and severity) and epilepsy-associated comorbidities (anxiety, depression, QOL, and measures of fitness/cardiovascular health) in the exercise group compared to the control group.

Methods and Measures

Design

A randomized, controlled trial with a two-arm, parallel group design with a wait-list education control



Setting

Academic medical center, Atrium Health Wake Forest Baptist

Subjects selection criteria

Adults with epilepsy will be actively recruited from the Comprehensive Adult Epilepsy Clinic at Atrium Health Wake Forest Baptist, and passively recruited from the community

Inclusion Criteria

•Age 18 or older
•Focal or generalized epilepsy, as determined clinically by a WFBH epileptologist with no significant consideration of an alternative diagnosis
•Active epilepsy with at least 1 observable seizure in the 6 months prior to screening
•Access to a smartphone with application capabilities
•Internet access or cellular data plan to attend virtual sessions

- Able to ambulate independently

Exclusion Criteria

- Diagnosis of nonepileptic or psychogenic spells
- Seizures associated with falls with injury (such as atonic seizures)
- Currently active >/= 30 min on 3 or more days per week or > 5000 steps/day during the baseline period
- Medical conditions that would limit ability to participate in an exercise intervention including:
    - Stage III or IV Congestive Heart Failure (CHF)
    - End-stage Renal Disease
    - Severe dementia or significant cognitive impairment that precludes participation in the intervention or limits ability to follow the study protocol
    - Uncontrolled hypertension (HTN) defined as systolic blood pressure greater than 180 mmHg and diastolic blood pressure greater than 110 mmHg at rest
    - Severe arthritis, amputations, or orthopedic problems that limit ambulatory ability
- Currently pregnant or plan to become pregnant during the study period (16 weeks)
- An active Central Nervous System (CNS) infection, demyelinating disease, degenerative neurologic disease or any CNS disease deemed to be progressive during the course of the study that may confound the interpretation of the study results
- Any clinically significant psychiatric illness, psychological, or behavioral problems that would interfere with the subject's ability to participate in the study.
- Unwilling or unable to comply with all study visits and procedures
- Participants who have <75% complete days of seizure recording in the study diary or step data via the Garmin device will not be randomized.

Sample Size

Up to 40 subjects will be enrolled, with a 2:1 ratio of intervention to control group randomization to best address aims 1 and 2.

Interventions and Interactions

All participants will wear a Garmin device and keep a study diary throughout the duration of the study. In addition, they will wear an ActivPAL 4 for 1 week at the end of the baseline, intervention, and maintenance periods. This will be mailed to them for each of the three recording periods along with written instructions (attachment 8).

Baseline Period: During a 4-week baseline period, the participants will continue their usual activity but will wear the Garmin and ActivPAL 4 and keep a study diary. We will use this to assess their baseline PA profiles and seizure frequency and to screen for adherence with device and diary use, as participants who have <75% complete days of seizure recording or step data via the Garmin will not be randomized. A 4-week baseline period and self-report of seizures are both standard protocol in epilepsy clinical trials.[45]

Batched enrollment will be utilized to ensure large enough groups for the group coaching exercise intervention. Due to this, the time between visits may vary.

Arm 1 Exercise Intervention:

Participants in this arm will undergo a 12-week physical activity program aimed to achieve the equivalent of 8,000 steps per day (56,000 weekly steps). To ensure uptake, our intervention is rooted in social cognitive theory and led by a trained health coach, trained within the Wake Forest Behavioral Medicine Lab's Behavioral Coaching program, which follows principles of group dynamics, social cognitive theory, and self-determination theory to develop self-efficacy for behavior change, which is instrumental to building lasting behavior.

Participants will meet in small groups of 2-8 participants facilitated by a behavioral coach and, when available, a patient-stakeholder. Following randomization, the behavioral coach will contact the participants in this arm, to set up a time for each weekly video meeting. Each weekly meeting will occur within the coach's locked Webex room using a single link that will be provided to participants digitally via email. In the event of any unforeseen technical difficulties, participants can call into the Webex meeting, but this is not preferred. These sessions are developed using group dynamics principles and founded in social cognitive theory, utilizing the group structure as a tool of behavior change. Participants will act as models to one another, provide an avenue for addressing exercise barriers that arise daily, and foster a sense of accountability toward weekly activity goals.

During each weekly video meeting, the coach and participants will review the timing of the next week's meeting, modifying the timing as needed, and setting reminders if applicable.

Each group session will progress through the following tasks:

1. **Introduction and ice breaker:** Participants will engage in brief tasks requiring self-disclosure as a means of opening communication for the remainder of the session.
2. **Didactic content:** Next, the coach will guide participants through weekly didactic content related to health and physical activity. These sessions are designed to reduce negative outcome expectencies related to activity (e.g., activity is unsafe, addressing how different types of movement improve health), to highlight facilitators in the environment while addressing common barriers to activity, and providing education on how activity improves health.
3. **Discussion**: Building on weekly didactic content, each session will end with a guided discussion designed to provide positive reinforcement of weekly successes, opportunities to address barriers as a group, and repertoire-development in which participants share exercise experiences they have enjoyed recently.

In addition to weekly group sessions, participants will communicatie briefly one-on-one with the behavioral coach using a medium of their choosing (webex, telephone, email) to address any private concerns and to review and revise goals. Key facets of these exchanges include:

1. **Review of the previous week's goal**: The coach will review with the participant progress toward the previous week's goal. To do this, the coach will log into the Garmin Connect website using the credentials provided to the participant by the study team. The coach will emphatically congradulate goal success—thus enhancing self-efficacy through mastery experiencess—and adopt a proactive tone during failures with the aim of mitigating feelings of guilt. During week 1, the conversation will instead center on understanding previous experiences with activity to guide selection of the initial goal.
2. **Selection of a new goal**: Participants will aim to progress in both intensity and duration over the course of the program. The participant and coach will select a progressive stepping goal that is challenging but attainable (increase in ~20-30% increments depending on baseline steps). They will objectively self-monitor progress toward step goals, a key self-regulatory behavior. Acheivement of goals is a key *mastery experience*, the most potent input to self-efficacy, and consistently identified as the key behavioral predictor of activity behavior.[46]. Goals will be revised weekly until at least 8000

steps/day is achieved *and* it is not feasible to continue increasing.When the individual fails to meet a weekly goal, conversation will center on identifying **true** barriers (e.g., where "too busy" is commonly cited as a barrier, this is assigned by the participant retrospectively, where momentary hunger or fatigue states were the true barriers), and then developing strategies for addressing these barriers. As appropriate, the coach may suggest the participant brings these barriers to group conversations. Goals will be progressed only following successful weeks. Maintenance goals will be set once participants achieve 8000 steps/day is achieved *and* it is not feasible to continue increasing.

Key theoretical constructs that are addressed within each communication include:

- **Verbal persuasion**: The coach will emphasize the term physical activity over exercise (negative implicit associations) and provide kind encouragement.
- **Intrinsic motivation**: The coach will emphasize methods of aerobic physical activity that are enjoyable, placing emphasis on walking behaviors. A key educational technique involves clueing participants into the "family" of walking behaviors, noting that there are different psychosocial benefits to social versus solo walking, urbana versus rural walking, and more. Conversations emphasize enhancing enjoyment the addition of a social component or enjoyable audio, structuring the activity so that it is enjoyable (e.g., walking in the morning, walking during lunch), and avoiding tying walking to unpleasant sensations.
- **Mastery**: Goal reviews will highlight and emphasize even small successes. Participants will be made to reflect weekly on their own successes and will be asked explicitly to savor these sensations while letting go of any perceived failures.
- **Interpretation of psychophysiological responses**: The coach will help individuals to re-interpret physical stimuli as needed (e.g., anxiety over elevated heart rate).
- **Outcome expectencies**: Discussions will target negative outcome expectencies around safety as they arise and downplay conventional ideas about "exercise".
- **Barriers**: The coach will not query for barriers to avoid generation of new barriers, but will troubleshoot barriers as they arise in a manner that is non-negative and action oriented. Conversations will guide the participant to self-discover strategies.
- **Facilitators**: The coach will include purposeful discussion of environmental and social facilitators during each session.

To ensure fidelity, the coach will audio/video record each group session, and these sessions will be spot checked by a member of the research team using a coaching checklist to ensure each theoretical element is being addressed. The coach will also self-rate adherence to these principles on a checklist following each session. This will serve as a second fidelity check, but will also continuously remind the coach of these important coaching principles.

The use of the Garmin for Goal Review and Selection

Prior to the start of the 1:1 session, the coach will sign into the Garmin Connect web page for the participant using the credentials provided to the participant from the study team. The coach will review step data and any exercise bouts ahead of time to estimate whether the participant achieved the previous week's goal. This will provide a sense of familiarity to the participant

during the phone call, and will also prepare the coach to troubleshoot Garmin usage for days with missing data.

Arm 2 Control:
Participants randomized to the wait-list attention control group will continue to undergo standard care for 12 weeks. They will contine to wear the Garmin activity tracker and can view their activity but will not be given an exercise program. They will be contacted by a study staff member via telephone every 2 weeks for health education. If for some reason they need to miss a session, the information will be emailed to them. During this time, they will review resources and healthy lifestyle guidelines for people with epilepsy, including healthy diet, medication compliance, seizure precautions, stress management, and sleep hygeine. At the end of study, if they complete all study visits, they have the opportunity to receive a personalized exercise program.

Changes to anti-seizure therapy (including medications or devices) during the study will be discouraged in both groups. However, participants who do report medication or device changes will be allowed to continue in the study but will be analyzed separately in the results. Medications and medication compliance will be reviewed at each study visit.

Strategies to support fidelity of the intervention:

- Design: This is a randomized trial of an exercise intervention in people with epilepsy. It is specifically designed to be a simple, individually tailored intervention that can be accomplished at home and measured easily with the use of a wearable device. This design supports the fidelity of the intervention and the ability to measure the fidelity using the device output instead of relying on self-report alone.
- Training: All coaches for the weekly virtual sessions will complete the Behavioral Coach Training provided by Dr. Fanning's Behavioral Medicine Lab. Coaching centers on effective communication and coaching methods to develop strong social bonds, self-efficacy, and intrinsic motivation for the behavior, thus enhancing uptake and maintenance of the behavior. In the final sessions of this training, coaches complete behavioral simulations to determine readiness to coach.
- Delivery: The brief social cognitive theory based module that is given at the start of each weekly session will be consistent for all participants. Strategies to revise and reset goals for the coming week will follow standard social cognitive therapy practice, as outlined in the training. Dr. Fanning and the coaches will meet at least once monthly to discuss participant progress and to ensure coaches are following evidence-based social cognitive practices in their communications with participants. Sessions will be recorded and Dr. Fanning will review a random session each month and provide feedback to the coach to ensure fidelity of the delivery. In addition, coaches will self-rate their coaching following each coaching session.
- Receipt: The instructors will observe participants during weekly virtual sessions to ensure they understand how to use their Garmin device.
- Enactment: The participants will use the practices learned in the weekly sessions to perform continuous walking in their home environment (or environment of their choice). Their activity will be recorded on the Garmin device and then revieiwed with the coach at the next weekly session.

Strategies to support adherence:

- Coaches will work with participants to set reminders for weekly sessions, and will follow-up for any missed contacts.
- Self-efficacy and socially-driven goal setting are the two key constructs driving activity adherence, and thus these are the focus of the coaching intervention.
- Participants with significant cognitive impairment (dementia) will be excluded from the study.
- The study intervention is simple and the weekly step goal is clearly explained to the participant.
- The weekly step goal is individualized, and is created each week during a 1:1 session with the coach while taking into account the participant's individual barriers.
- Participants will be encouraged to seek social support from family and friends and walk with family and friends when able.
- The intervention period is relatively short (only 12 weeks).
- Participants in the control group will be given a personalized physical activity plan if they complete the study
- All participants will be compensated $50 per visit (4 visits; for total of $200/participant) to help cover the costs of transportation, parking, and any time away from employment for each research visit.
- Eligibility criteria are designed to exclude participants in poor physical or emotional health for whom adherence may be challenging.
- Study appointment reminders will be given to all participants. Reminders to complete the study diary will be given daily.
- For in-person study visits, the participant will be contacted 1-3 days prior to remind them and confirm the appointment.
- The group coaching format will enhance social support, participant engagement, and add additional resources to help with troubleshooting barriers. When available, a patient-stakeholder will join the coaching session to provide additional social support.

Strategies to support retention:

- Participants in the control group will be given the opportunity to receive a personalized physical activity program if they complete the study.
- Participants will be compensated $50 per study visit V1-V4
- Study appointment reminders will be given to both groups.

BLINDING
Due to the nature of the intervention, participants will not be blinded as to whether they are in the intervention or control group.
The final analysis of activity data and heart rate variability (HRV) will also be performed by blinded assessors. An unblinded investigator or sub-investigator will gather the data and de-identify the information such that those processing the data will not be privy to which arm is which. The PI will not be blinded in this pilot feasibility study, in order to best track adherence and fidelity and help troubleshoot unexpected barriers.

FOLLOW-UP VISITS
Visit 3, Week 16 End of Intervention:
At the end of the intervention period, participants will return for post-intervention assessments to include assessments of seizure frequency (Study Diary), seizure severity (Liverpool Seizure Severity Scale), depression(NDDI-E), Review Assurance of the NNDI-E, anxiety (GAD-7), quality of life (QOLIE-31), medication side effects (AEP) cardiorespiratory fitness and mobility (maximum oxygen uptake and 6 minute walk test), sleep (PSQI and from Garmin device) and autonomic tone (heart rate variability).

At the end of the intervention period, participants in arm 1 will be encouraged to continue their current habits. Participants in arm 2 will be offered the opportunity to receive a personalized exercise program. Those in arm 1 will also complete a questionnaire about the acceptability, tolerance and satisfaction with the exercise intervention.

Visit 4, Week 28. Sustainability Follow-up and Study end
This will be a remote visit in order to reduce exposure in the era of COVID-19 as well as improve access for PWE. All outcomes will be re-assessed for sustainability, with the exception of the exercise test, HRV and the 6MWT due to the remote nature of this visit. The risks of excessive in-person visits and transportation issues outweigh the potential benefit of collecting this follow-up data, especiallyin light of COVID-19. At the end of the visit, all participants will answer an exit questionnaire on their thoughts about the study, what they liked, and what they would change.

All visits will occur either at the Worrel Building or at the Clinical Research Unit (CRU). Due to batched enrollment, time between visits (especially Visits 2 and 3) may vary.

	Visit 0 Telephone Screen	Visit 1 Enrollment Week 0	Visit 2** Randomization Week 4	Intervention Period Week 5-16		Visit 3 End Intervention Week 16	Visit 4 Follow-up Week 28 (remote)
				Exercise	Control		
Review inclusion/exclusion	X	X					
10 meter walk screen		X					
Informed Consent		X					
Vital Signs		X				X	
Collect demographic and baseline medical information		X					

Distribute Study Diary		**X**					
Distribute Activity Tracker		**X**					
Collect/Review Study Diary*			**X**			**X**	**X**
Collect/Review data from Garmin			**X**	**X**	**X**	**X**	**X**
Review medications and adherence		**X**	**X**			**X**	**X**
Randomization			**X**				
Weekly telehealth coaching				**X**			
Intervention satisfaction questionnaire				**X**			
Telephone education Q2 weeks					**X**		
Exercise Test			**X**			**X**	
Questionnaires: PSS, AEP, NDDI-E, Review Assurance of the NNDI-E, GAD-7, QOLIE-31, EXSE, EGS, MOESS, LSSS		**X**				**X**	**X (with exception of NDDI-E and "Review Assurance of the NNDI-E")**
HRV measurement		**X**	**X**			**X**	
6 minute walk test		**X**				**X**	
Exit Questions							**X**

*in addition to review at these visits, the study diary will also be returned daily and reviewed by weekly by a member of the study staff.

**If scheduling is a challenge, V2 can be completed over the telephone with the exercise test being conducted at the first available timepoint and prior to the intervention period

Outcome Measure(s)

1. Primary Objective: Feasibility of the intervention (Adherence and Sustainability)
    a. Primary Endpoints
        i. Adherence to the intervention
        Adherence will be measured as the number of average daily steps achieved compared to steps assigned during the final 4 weeks of the intervention period
        ii. Sustainability of the intervention
        Sustainability will be measured as the number of average daily steps achieved compared to steps assigned during the final 4 weeks of the maintenance period
2. Secondary Objectives: To evaluate the intensity distribution in the intervention arm
    a. Secondary Endpoints: time spend in various activity behaviors (measured by the ActivePAL4)
        i. Time spent sedentary
        ii. Time spent in light intensity activity
        iii. Time spent in moderate intensity activity
        iv. Time spent in vigorous intensity activity
        v. Acceptability of the Intervention
        Participants will answer an exit survey at Visit 4 regarding what they liked about the study and what they did not like, including reasons for missed visits or non-adherence, barriers encountered, and overall satisfaction of various aspects of the study. In addition, arm 1 will answer a questionnaire at the end of the 12 week intervention about the acceptability, tolerance and satisfaction

with the exercise intervention. For the main endpoint, we will use the question "How satisfied were you with the exercise intervention?" with scale of 1=VERY UNSATISFIED, 2=UNSATISFIED, 3=NEUTRAL, 4=SATISFIED, 5=VERY SATISFIED. We will calculate the proportion of subjects who answer 4 or above.

3. Exploratory Objectives: Exploratory Effectiveness: For exploratory efficacy purposes, we will also gather pre- and post- intervention data on seizures, depression, anxiety, physical functioning, quality of life, and social cognitive mediators of behavior change via the following:
    a. Exploratory Endpoints
        i. Effects on seizures
            1. Seizure frequency via study diary report
            This has been shown to be a reliable and standard way of recording seizures in epilepsy studies. For the purposes of evaluating a change in seizure frequency, the number of seizures during the final 4 weeks of the intervention will be compared to the number of seizures during the 4-week baseline. The diaries will be returned via electronic data capture in redcap. Participants will be reminded to complete and return the diary via automated text and/or email. If diaries are not received, the participant will be called and prompted to return the study diary.
            2. Seizure severity via the Liverpool seizure severity scale (LSSS)
        ii. Effects on mood:
            1. Depression scores
            Participants will complete the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)[47]. This will be performed in-person at visits 1 and 3 only (monitoring and management of expression of suicidal ideation is outlined under Section VI below). This will be reviewed by study personnel and documented in the *Review Assurance of the NNDI-E* form
            2. Anxiety scores
            Participants will complete the Generalized Anxiety Disorder (GAD-7)[48, 49]in person at Visits 1 and 3 and remotely via redcap survey at Visit 4.
            3. Stress scores (PSS)
            Participants will complete the Perceived Stress Scale (PSS) in person at Visits 1 and 3 and remotely via redcap survey at Visit 4.
        iii. Effects on quality of life
            1. Quality of Life
            Participants will complete the Quality of Life in Epilepsy-31 (QOLIE-31)[50]. This will be given in person as Visits 1, and 3, and remotely via emailed redcap survey link at Visit
            2. Medication side effects
            Participants will complete the Adverse Event Profile (AEP) at Visits 1 and 3 and remotely via emailed redcap survey link at Visit 4
        iv. Effects on social cognitive theory constructs
            1. To evaluate the influence of social cognitive constructs on behavior change in this population, participants will complete the Exercise Self-

Efficacy Questionnaire (EXSE)[51], Exercise Goal Setting Questionnaire (EGS)[52], and Multidimensional Expectations for Exercise Scale (MOEES)[53]. These will be given in person at Visits 1 and 3 and remotely via redcap survey at Visit 4.

2.

v. Effects on physical function
    1. Autonomic tone: Heart rate variability (HRV)
        a. Heart Rate Variability (HRV) measurement: Continuous heart rate will be recorded while the participant is breathing normally in seated position for 10 minutes using Faros 180 heart rate monitor (Bittium Corporation, Oulu, Finland)[54]. Beat to beat intervals (RRI) files will be generated at 1000 Hz via the data acquisition software. The files will be analyzed with Nevrokard HRV software (by Nevrokard Kiauta, d.o.o., Izola, Slovenia). The recordings will be visually inspected to ensure data quality (dropped beats or gross motion artifacts are excluded) and the first 5 minutes of usable tracings will be analyzed. We will obtain measures of HRV in the frequency domain and these measures will be integrated over specified frequency ranges (LF: 0.04-0.15 Hz; HF: 0.15-0.4 Hz). Power of RRI spectra in LF, HF range (LFRRI and HFRRI) will be calculated in normalized units and the ratio of LFRRI/HFRRI will be used as a measure of sympatho-vagal balance. We will also calculate the standard deviation of normal-to-normal interval (SDNN) and the root mean square of successive differences (RMSSD) indexes, given their established study in PWE.[11, 12]
    2. Cardiorespiratory Fitness:
        a. Maximum oxygen uptake (VO2 max)
            i. Cardiopulmonary exercise test using a modified Balke protocol[55, 56] on a treadmill
        b. 6-minute walk test (6MWT)
        Participants will undergo a 6 minute walk test at Visits 1 and 3, according to established guidelines[57]. This is a is cost-effective and well-documented field test for assessing functional exercise capacity and response to medical interventions in diverse patient groups, and predicts cardiorespiratory fitness among healthy people[58].
    3. Sleep:
        a. Nightly average total sleep time (TST): will be collected from the Garmin activity tracker
        b. Sleep quality will be assessed via the Pittsburgh Sleep Quality Index (PSQI)
        c.

Analytical Plan

Aim 1 To assess Feasibility, we will look at (1) adherence and (2) sustainability. Adherence, defined as the proportion of participants who achieve their assigned step goal (as measured by average daily steps via the Garmin device) over the last 4 weeks of the intervention period, will be calculated and 95% binomial confidence intervals generated. Sustainability will be calculated similarly for the final 4 weeks of the maintenance period. In each case, we will utilize a one-sided 95% confidence interval to estimate the lower bound for adherence and sustainability rates to inform future studies.

Aim 2 To assess exercise *intensity,* we will use descriptive statistics to describe the time spent in sedentary, light, and moderate to vigorous PA. We will generate confidence intervals to evaluate if the achieved intensity is within the range recommended by the AHA (150 min of moderate or 75 min of vigorous activity per week).[59] To assess acceptability, arm 1 will answer a questionnaire at the end of the 12 week intervention about the acceptability, tolerance and satisfaction with the exercise intervention. For the main endpoint, we will use the question "How satisfied were you with the exercise intervention?" with scale of 1=VERY UNSATISFIED, 2=UNSATISFIED, 3=NEUTRAL, 4=SATISFIED, 5=VERY SATISFIED. We will calculate the proportion of subjects who answer 4 or above.

To address Aim 3 (exploratory evaluation of effects epilepsy and epilepsy associated comorbidities), we will compute change scores in seizure frequency, severity (LSSS), anxiety (GAD-7), depression (NDDI-E), medication side effects (AEP), cardiorespiratory fitness (VO2 max and 6MWT), heartrate variability (HRV), sleep (total sleep time per night) and quality of life (QOLIE-31) pre- and post-intervention. We will use multivariable linear regression models modeling change score as the outcome, with intervention assignment as the main effect of interest and baseline scores as a confounding variable. We will use estimates of the effect sizes and variability for planning and power of a larger trial. For HRV parameters, we will look at high and low frequency indices, standard deviation of normal-to-normal interval (SDNN) and the root mean square of successive differences (RMSSD) indices, given their established study in PWE.[11, 12]

Similarly, we will explore for effects on social cognitive mediators of behavior change (scores on EXSE, MOEES, and EGS), following the same modeling approach.

Human Subjects Protection

Subject Recruitment Methods

In order to ensure optimal recruitment, eligible subjects may be identified from the below recruitment pools. Potentially eligible subjects from the groups below will undergo further chart review to refine eligibility criteria by reviewing the following: age, epilepsy diagnosis, seizure type and frequency, ambulation status, medical history, and medications. In order to confirm eligibility of patients, the study team may review local charts or may ask the patient for copies of their local medical record (only the minimum amount of information will be collected by the study team to ensure a diagnosis of epilepsy).

Preliminarily eligible subjects will be contacted via telephone call from study staff, approached in person during their epilepsy clinic visit or EMU stay, or sent a message via mywakehealth. If the patient is not reached by phone, these individuals will receive, through mail, a letter from clinical PI asking them to contact us if interested in participating in the study. Once the patient is reached, a verbal screening consent will be obtained, allowing study staff to ask only screening questions including age, seizure frequency, ability to ambulate without difficulty, history of seizures associated with frequent falls or loss of muscle tone, current exercise habits, presence of end-stage CHF, ESRD, severe dementia, or presence of high blood pressure that is not controlled with medications (over 180/110) (Refer to phone screening script for further details). If contacted via an DComm approved message in mywakehealth, the participant can reach out to study staff via phone or email, or choose to click on a redcap link for more

information and to answer a small subset of preliminary screening questions ("do you have epilepsy" and "have you had at least 1 seizure in the past 6 months"). From here, preliminarily eligible participants will leave their contact information (phone number and/or email address) and, if eligible by chart review, subsequently be called by a member of the study team to perform the complete telephone screen.

Demographic information on the participants age, race, gender, seizure frequency, medications, history of epilepsy surgery, employment status, address, and distance from the exercise facility will be recorded on all screened subjects. If eligible and willing to participate, the email and/or mailing address will be recorded in order to mail or email a copy of the consent form for optional review prior to the enrollment visit. For ineligible participants, the reason(s) for ineligibility will be recorded. For eligible participants who decline to participate, we will also record the reason for declining.

- Chart review study: Potentially eligible subjects have been identified through a recently conducted chart review (IRB00056209). This database contains over 800 charts from approximately April to October 2018 at WFBH Adult Epilepsy Clinic. Charts have been screened for seizure frequency, cognitive level and ambulatory status. Preliminarily eligible patients may be contacted via the procedures described above.
- Cross-sectional survey: Potentially eligible subjects have been identified through a recently conducted survey (IRB00062580) in the WFBH Adult Epilepsy Clinic and the adult Epilepsy Monitoring Unit (EMU). Participants were surveyed regarding their seizure frequency, baseline activity habits, and interest and ability to participate in a monitored physical activity intervention. They also indicated their willingness to be contacted for future studies. Preliminarily eligible patients may be contacted via the procedures described above.
- Observational survey: Potentially eligible subjects will be identified through a recently conducted observational study (IRB00062034) using wearable devices to track activity and sleep in epilepsy. In this study they also indicated their willingness to be contacted for future studies. Preliminarily eligible patients may be contacted via the procedures described above.
- Prior pilot study: (IRB00068408) participants who were screened for this study but were not eligible or did not enroll will be identified from the existing screening database and examined for eligibility. Preliminarily eligible patients may be contacted as described above.

•Further eligible participants will be identified by prospective chart review of all epilepsy patients presenting to the adult epilepsy clinic each week for outpatient appointments (in-person or telehealth) or epilepsy monitoring unit admissions. We will review the chart for eligibility. Preliminarily eligible patients may be approached in clinic by a member of the study team and screened for eligibility or contacted via the procedures described above. Any potentially eligible participants communicated to the study team via word of mouth may also be contacted as described above.

Eligible subjects who agree to participate will be scheduled for V1 Enrollment. They will be mailed or emailed a copy of the consent form and a study overview handout (attachment 3) to review prior to enrollment.

In addition, the study will be added to the "Be Involved" website of WFBMC with contact information of the study staff. Interested participants who email or call will undergo the telephone screening process described above. Informational flyers will be hung in each room in the adult epilepsy clinic (again with contact information), inpatient Epilepsy Monitoring Unit, and displayed at the monthly epilepsy support group meetings. Lastly, an informational flyer with contact information will be posted on the Epilepsy Alliance of North Carolina's website. Flyers may also be distributed throughout the community and at other health clinics in the surrounding areas.

Informed Consent

Signed informed consent will be obtained from each subject. Consent will be obtained by a

member of the study staff at the enrollment visit. Those who are scheduled for an enrollment visit will be mailed and/or emailed a copy of the informed consent document for optional reading prior to enrollment.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed 6 years after study completion by deleting the linkage file, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

In group meetings with participants, respect for the privacy and confidentiality of other group attendees will be emphasized.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff. A Data Safety and Monitoring Committee, an independent group of experts, will be reviewing the data from this research throughout the study

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

SAFETY AND MONITORING PLAN

Adverse Event Definitions:

Adverse Event: (AE) For the purposes of this trial an adverse event is defined as any untoward or unfavorable medical occurrence that is temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Expected Events: In this study, no serious adverse events are expected. Expected adverse events include temporary muscle soreness, temporary joint pain, and temporary increased physical fatigue when starting the exercise regimen or when increasing the exercise. Other expected events include mild discomfort from physical exertion including shortness of breath that improves when ceasing exercise and sweating. In people with asthma, an increase in the need for inhaler use is expected. In people who have a very high baseline seizure frequency, and even in those with less frequent seizures, seizures are reasonably expected to occur during exercise on occasion and certainly will occur during the course of the study. However, seizures that occur consistently with exercise in a single individual is not expected. In addition, it is not expected for participants to have a large

increase in seizure frequency. A small increase would be within the normal fluctuation of seizure frequency in people with epilepsy.

Specifically, the temporal relationship of seizures to exercise will be recorded in the daily study diary. Responses will be reviewed by the study team weekly. In participants who demonstrate an increase in seizure frequency from their baseline weekly frequency consistently over a 4 week period, the temporal relationship to exercise will be further investigated. In those who have increased seizure frequency AND who report a clear temporal association with exercise (seizure occurs during or immediately after exercise in 50% or more of their seizures), participation in the intervention will be halted due to concern for exercise-induced seizure activity.

All other events not listed above will be considered unexpected for the purposes of this trial. The unblinded investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Adverse Event Classification:
All AEs will be assessed by the study staff for severity and categorized using the criteria described below.

Serious Adverse Events: (SAE) Any event that results in death, hospitalization or prolongation of a hospitalization, significant or persistent disability, a birth defect or congenital anomaly, or another significant event or problem requiring medical or surgical intervention to prevent one or more of the above.

General Adverse Events:

Mild Adverse Events: Events that require minimal or no treatment and do not interfere with the participant's daily activities.

Moderate Adverse Events: Events result in a low level of inconvenience or concern with t the therapeutic measures. Moderate events may cause some interference with functioning.

Severe Adverse Events: Events that interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

All adverse events will also have their relationship to study intervention assessed by one of the co-investigators (un-blinded) who will examine and evaluate the participant based on temporal relationship and his/her clinical judgment and categorized into one of the following:

Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically

plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Potentially Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Unlikely to be related: A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

Not Related: The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

Adverse Event Tracking:

Adverse Events that are of special interest for this study will be actively tracked. These include worsening of seizure frequency, falls, and injuries. These will be specifically recorded by the participant in their study diary, which will be returned electronically daily.

All other adverse events will be passively collected at each study visit (visits 2-4) by asking "have you had any health problems since your last visit?"

All AEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring during the study must be documented appropriately regardless of relationship.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Management of Suicidal Ideation:
Given the nature of NDDI-E as a depression screening tool, question 4 pertains to passive suicidality. If participants score a 3 or 4 on this question, follow-up questions will be carried out by study staff, to determine any possibility of active suicidality. If there is a need for immediate treatment (e.g., active suicidal ideation, active psychotic symptoms, disorientation, active substance abuse) at any point in time, staff will follow the in-person crisis procedures included in Appendix A. If, during a remote visit, a participant voluntarily expresses suicidal ideation, we will follow the established crisis procedures under the remote protocol in Appendix A. Follow-up questions and any immediate treatments will be documented in the "Review Assurance of the NNDI-E" form.

As a safety precaution, we will ask each participant upon study enrollment to identify 1 persons whom we can contact in case of an emergency and provide a telephone numbers for this individual.

If suicidality is expressed, we may notify their outpatient neurologist in order to help guide future care.

Because this is not a treatment study, and given the low rate of active suicidality previously identified during a Wake Forest Baptist Health learning health system trial led by Dr. Munger Clary (included screening more than 760 individuals using the NDDI-E instrument), we anticipate that active suicidality will be exceedingly rare. All study staff will receive training on the crisis protocol and will have regular meetings with the team to discuss clinical issues.

Management of Seizures:
The principal investigator will provide training to all study staff regarding seizure management and seizure first aid. Staff will be informed the proper way to care for the patient during the acute seizure period including how to keep the patient from injuring themselves, how to time a seizure, and when to call for help. The PI will be notified in all instances to provide further guidance. Staff will follow outlined safety procedures on when and how to contact any necessary additional emergency care. It should be noted that most seizures do NOT require emergency care and will resolve on their own, but staff will be trained to respond to all scenarios. Participants will always be advised to notify their primary outpatient epilepsy physician of any seizures and this provider will guide long-term management of their care.

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Appendix

1. Copies of each questionnaires or surveys that will be used
    a. AEP
    b. PSS
    c. NDDI-E
    d. GAD-7
    e. QOLIE-31
    f. EXSE
    g. EGS
    h. MOEES
    i. Exercise Satisfaction Survey
    j. Exit Survey
    k. Liverpool seizure severity scale
    l. PSQI
2. Consent form
3. Study Overview Handout
4. Crisis Procedures – Appendix A
5. Control group scripts:
    a. Healthy eating script,
    b. Medication script
    c. Emotional Health script
    d. Stress script
    e. Sleep script
    f. Seizure diary script
6. Garmin Operating Instructions
7. ActivPAL log and operating instructions
8. Telephone screening script
9. Study Advertisement
10. Study Diary
11. Coaching manual for the intervention group
12. Webex instructions
13. Handout for group instructions after randomization