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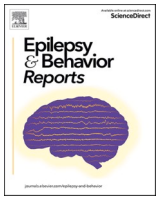

Developing optimized physical activity interventions for drug-resistant epilepsy: Challenges and lessons learned from a remote exercise intervention pilot trial

Halley B. Alexander [a,*], Heidi M. Munger Clary [a], Hossam A. Shaltout [c], Nathan B. Fountain [d], Pamela Duncan [a], Peter Brubaker [b], Jason Fanning [b]

[a] Wake Forest University School of Medicine, Department of Neurology, Winston-Salem, NC, USA
[b] Wake Forest University, Department of Health and Exercise Science, Winston-Salem, NC, USA
[c] Wake Forest School of Medicine, Hypertension and Vascular Research Center, Winston-Salem, NC, USA
[d] University of Virginia, Department of Neurology, Charlottesville, VA, USA

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ABSTRACT

People with epilepsy (PWE) stand to benefit significantly from increasing their physical activity, but promotion of physical activity is difficult in any population; a challenge compounded by the unique barriers encountered by PWE, especially those with drug-resistant epilepsy (DRE). This study explores the feasibility of a remotely delivered, 12-week aerobic exercise program based on social cognitive theory principles in adults with DRE. This line of research is nested within the Multiphase Optimization Strategy (MOST), a framework that emphasizes iterative early pilot work (preparation phase research), followed by iterative optimization phase research. Ten participants were recruited, and four out of ten completed the study, resulting in 3.8 % recruitment from those preliminarily eligible by chart review, and 40 % retention. While acceptability was high among those who completed the study, recruitment, retention, and uptake were low. Three key related lessons learned emerged: 1) low appeal of an exercise intervention in our population of DRE 2) barriers related to comorbid mental health struggles, and 3) fear of seizures. How to best approach physical activity promotion in PWE, particularly DRE, will require a somewhat novel approach involving iterative pilot work and optimization before large scale efficacy trials and implementation can be achieved.

1. Introduction

People with epilepsy (PWE) stand to benefit significantly from increasing their physical activity. In addition to the obvious anticipated benefits to cardiovascular health and mortality, physical activity may help improve mood, sleep, and cognitive disorders [1–5], all of which have an increased incidence in PWE [6–8]. These common associated disorders can have an even greater negative impact on health related quality of life (HRQoL) in PWE than the seizures themselves [9] but are often under-recognized and undertreated. In fact, many commonly used antiseizure medications have the potential to worsen these conditions. In addition to the expected beneficial effects on common comorbid conditions, animal studies and small studies in humans show that physical activity may reduce seizure frequency and is a possible complementary therapy for seizure control in PWE, with the potential to improve epilepsy across all aspects of the disease [10–12].

PWE generally believe that physical activity is good for their health, but they are more sedentary than the general population and less likely to meet the minimum recommended levels of physical activity [13]. PWE report specific barriers to physical activity, such as lack of transportation/driving restrictions, fear of seizure, stigma, and discouragement from family, friends, or medical providers [14–16]. It is also suspected that other factors such as high rates of comorbid depression and anti-seizure medication side effects such as sedation or dizziness may affect physical activity engagement.

Physical activity has myriad benefits for human health, and yet the promotion of physical activity is difficult in any population [17]. This challenge is compounded by the strong intrapersonal and structural barriers encountered by PWE. One potential strategy for extending exercise programming—a potentially efficient means of achieving physical

* Corresponding author at: 1 Medical Center Blvd, Department of Neurology, Janeway Tower, 9th Floor, Winston-Salem, NC 27106, USA.
E-mail address: halexand@wakehealth.edu (H.B. Alexander).

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activity recommendations—to PWE is via videoconferencing, which facilitates theory-driven intervention delivery by a coach (a key social support element in successful behavioral interventions) while extending reach to those with barriers to participation in in-person programming. A social cognitive theory based physical activity intervention involving videoconference delivery and real-time activity feedback via activity monitors demonstrated improved physical activity and decreased sedentary time in older adults with chronic pain [18,19], but to-date no such theory-based activity interventions exist specifically for PWE.

The purpose of the present study was to explore the feasibility and acceptability of a remotely delivered, 12-week aerobic exercise program based on social cognitive theory principles [20] in adults with drug-resistant epilepsy. This line of research is nested within the Multiphase Optimization Strategy (MOST), a framework for guiding a research program that emphasizes iterative early pilot work (preparation phase research), followed by iterative optimization phase research designed to efficiently test potential active intervention components [21]. Efficacy is then evaluated in a traditional parallel randomized controlled trial design only once effective components have been identified and refined. The findings presented herein are preparatory in nature such that they are intended to identify and refine potentially effective or ineffective components to retain for future optimization studies.

2. Methods

2.1. Study design

This was a randomized, controlled, parallel arm, single blind study of a physical activity intervention for PWE with an education control. It was conducted at a single center at a level 4 epilepsy center in the southeastern United States. The clinical trial was registered at ClinicalTrials.gov NCT04607317. The institutional IRB approved the study protocol and procedures. The overall study design consisted of a 4-week baseline period followed by a 12-week intervention period, and a 12-week maintenance period (Fig. 1).

2.2. Study participants

Participants were recruited between February 2021 and May 2022 by way of advertising flyers, chart review to identify potentially eligible participants, and participants from previous studies who agreed to be contacted for future research. Potentially eligible participants as determined by chart review were 18 years old or older, had a diagnosis of drug-resistant epilepsy (DRE, defined as failure to become and stay seizure-free despite adequate trials of 2 or more appropriately chosen and appropriately used anti-seizure medications) [22], and a seizure frequency of 1 or more observable seizures per month. Participants were excluded by chart review if they had a diagnosis of psychogenic non-epileptic attacks, were nonverbal or had significant cognitive impairment that would limit ability to participate, or were non-ambulatory. Preliminarily eligible participants were then contacted for additional screening and were excluded if they were already physically active 90 min a week or more or had comorbid medical conditions that would limit their ability to exercise safely. We also allowed for caregivers to engage in enrollment procedures, though the intervention was delivered on a 1:1 basis to the PWE. Participants underwent a 10-meter walk screen to determine ambulatory ability and were excluded for gait speed < 0.6 m/second to ensure adequate physical capacity [23,24]. This was in lieu of formal exercise testing, which was not able to be performed due to restrictions on aerosolizing procedures due to COVID-19.

2.3. Exercise intervention

The intervention was delivered remotely as to accommodate one of the most common reported barriers to physical activity in PWE: lack of transportation [14]. Participants in the exercise group participated in weekly 1:1 video coaching meetings with a behavioral health coach (interventionist). The timing of the weekly session was determined by each individual participant's schedule but was consistent from week to week. These meetings served to provide (1) didactic content related to physical activity behavior change among PWE; (2) social support and the opportunity to troubleshoot barriers; and (3) discussion with the coach to set and revise weekly activity goals. No exercise was performed during the sessions. Instead, participants worked with the coach to progressively increase time spent in moderate to vigorous aerobic physical activity throughout the week, with the goal of reaching 150 min per week in the participant's individualized target heart rate range, as per the American College of Sports Medicine guidelines [25]. While walking was the standard recommended activity based on prior research on activity preferences for PWE [14], participants were allowed to achieve the target outcome – minutes per week the target aerobic heart rate zone – with any activity they desired.

The base prescription began at 10–15 min of activity at 40–50 % of heart rate reserve (HRR) as estimated by the maximum heart rate (max HR) obtained from the baseline 6-minute walk test (HRR = max HR – resting HR). The aim was to progress to up to 30 continuous minutes at 60–70 % of HRR by week 6. Goals were modified in collaboration between participants and the coach to ensure they were challenging but attainable. Each week, the coach reviewed the Garmin activity monitor data to evaluate the participant's progress toward their, set goal and goals were subsequently refined weekly during the 1:1 meetings depending on participant success. Maintenance goals were set once participants achieved 30 continuous minutes at 60–70 % HRR. Additionally, in the conduct of the study it became apparent that bouted exercise goals were overly burdensome to several participants and dissuaded participation in physical activity. Thus, the coach added a secondary goal for these participants in the form of a daily step goal, which followed the same principles as above: it was based on their baseline stepping behaviors and increased progressively through collaborative goal setting.

The intervention was guided by principles of social cognitive theory and self-determination theory with an emphasis on bolstering self-efficacy via progressive goal attainment rooted in objective behavioral feedback, and developing positive outcome expectations for physical activity while reducing perceived barriers [20,26,27] (Fig. 2A). These are evidence-based strategies that have been leveraged with success for

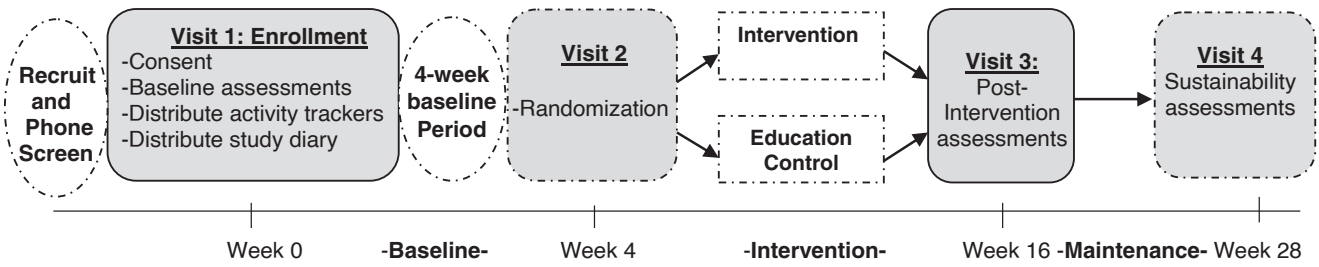
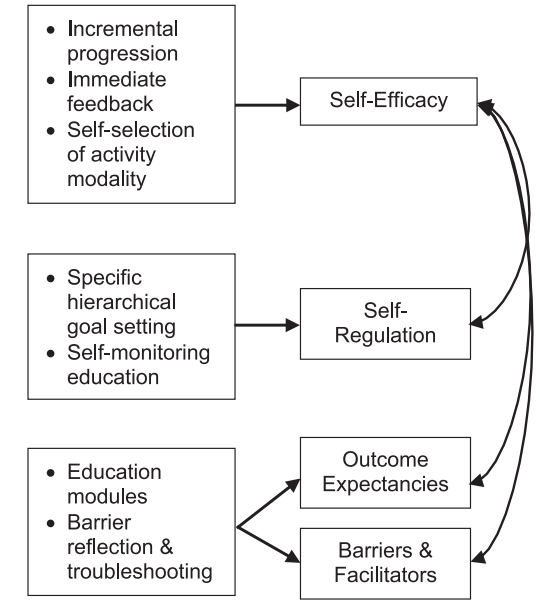


Fig. 1. Overall study design. Only the sections in solid outline (Visits 1 and 3, pre- and post-assessments) are performed in-person. All other elements (dashed outlines) are conducted remotely.

A



B

Week	
1	Introduction
2	Get Moving / Expected health benefits and intrinsically motivating activities
3	Winning the Battle with Barriers / Troubleshooting barriers and normalizing missed goals
4	Taking Stock / Recap and celebrating achievements, reflection.
5	Emotions / Science of emotions and how they affect our body
6	The Power of Thought / Cognitive distortions and challenging negative thoughts
7	Relaxing to Heal Your Body / The stress response and ways to manage it
8	Accountability / Sharing goals with friends and family and staying accountable
9	Taking Stock / Reflect on progress and create action plans
10	The Dynamic Nature of Behaviors / Internal and external factors that affect our activity
11	A Focus on Facilitators / Appreciating things that make being active easier
12	What to Expect on Your Own / Setting future goals and creating a tool-kit for the future

Fig. 2. A.) Concept diagram of key intervention techniques and the social cognitive targets they target. B.) Weekly coaching session content targeting social cognitive and self-determination theory.

physical activity promotion in several other populations [28–30]. For example, as noted above each weekly coaching session included a review of Garmin data and discussion on the previous week's activity and progress toward the previous week's goal with a focus on emphatically congratulating goal success—designed to enhance self-efficacy through mastery experiences and verbal persuasion. In the event the participant did not achieve their goal, the coach adopted a positive tone and centered the conversation on setting strategies to address barriers in the coming week. Following goal review and selection, the coach would guide the participant through weekly didactic content related to health and physical activity. These sessions were designed to reduce negative outcome expectancies related to activity (e.g., activity is unsafe), to highlight facilitators in the environment while addressing common barriers to activity, and to provide education on how activity improves health (Fig. 2B). To promote uptake and adherence, coaches also worked with the participants to help them choose aerobic activities that they find enjoyable and therefore intrinsically motivating, based on evidence that intrinsically motivated activities are more likely to be adopted and maintained [27,31,32]. For example, in this study, participants chose activities that included swimming and a kick-boxing class based on their enjoyment of these activities. Lastly, participants were encouraged to set reminders and to seek social support from family and friends.

Participants in the education control group continued standard care for 12 weeks. As in the intervention condition, control participants received a Garmin activity tracker and were able view their activity on the Garmin account, thus the study design controlled for any effect of device receipt. However, they were not given a physical activity program or health coach. Instead, they were contacted by a member of the study team via telephone every two weeks for healthy living education, which included a review of: healthy diet, medication adherence, seizure precautions, stress management, and sleep hygiene.

2.4. Assessments

As a pilot feasibility trial, our primary outcome was feasibility of recruitment and retention. Recruitment percentage was calculated as the number of participants enrolled divided by the total number who were potentially eligible with an a priori goal of 10 %. Retention was calculated as the percentage of all participants who complete the post-intervention assessment out of the total number of participants enrolled, with an a priori goal of 70 %. Efforts to maximize retention included participant compensation for time and travel for each completed assessment visit (Visit 1, 2, 3, and 4), appointment reminders, and opportunities to reschedule. Participants were determined lost to follow-up (LTFU) after 10 unanswered attempts were made to reach them and their listed secondary contact person. Secondary aims included uptake of the intervention defined as the proportion of participants in the intervention group who achieved their assigned heart rate target for at least 80 % of their prescribed weekly minutes (as measured by the Garmin activity monitor). The a priori target was to have at least 70 % of participants in the intervention group achieve this for at least 10 of the 12 weeks. Finally, we explored acceptability and possible moderators of uptake such as seizure frequency and baseline measures of anxiety, depression, stress, and self-efficacy.

All pre- and post-intervention assessments were performed during a single visit, which occurred immediately before or after the intervention period, in the following order: vital signs, six-minute walk test, questionnaires.

2.4.1. Physical activity measures

All participants wore a Garmin Forerunner 45 activity monitor on the non-dominant wrist throughout the duration of the study. They were instructed to wear it continuously, day and night, except when charging, which was required for ~30 min every 3–5 days depending on use. The Garmin device was linked to a de-identified research account and as such the research team was able to monitor physical activity as well as adherence with wearing and syncing the device. Garmin activity monitor data were leveraged as a proxy for adherence to the activity protocol. Garmin devices provide data on "moderate" and "vigorous" intensity minutes using a proprietary algorithm based on measured resting heart rate and demographic data and it is notable that participants were given a standard user profile (including a standard height, weight, age, and sex) to enhance privacy. The Garmin Forerunner 45 also requires a minimum moderate and vigorous intensity activity bout

duration of 10 min to count toward daily totals. Each minute spent at an estimated vigorous intensity is then doubled such that each minute moving at a vigorous intensity counts as the equivalent of two moderate minutes per the Garmin algorithm. For the purposes of this study, in line with standard activity monitoring practices, we wished to quantify minutes spent in any moderate-or greater intensity activity, thus we computed time spent in moderate-to-vigorous intensity activity (MVPA) as moderate intensity minutes + (vigorous intensity minutes/2). Days were counted as achieving one's goal if time spent in bouted MVPA equaled or exceeded their goal duration. For daily step goals, days were counted as achieving one's step goal if a participant's daily step total (as recorded from the Garmin device) was equal or greater than their target step goal. Days with < 250 steps were considered non-wear days and were excluded from the analysis. Weeks with < 3 valid days of wear were excluded.

The six-minute walk test was used as a measure of cardiorespiratory fitness and was performed pre- and post- intervention according to standard guidelines [33,34]. Heart rate (HR) immediately after the six-minute walk test was used to calculate maximum heart rate (Maximum HR = six-minute walk test HR/0.80) to determine the intensity prescription of the exercise [35].

2.4.2. Acceptability

Acceptability was measured by the exercise satisfaction questionnaire, which was completed by participants in the exercise intervention arm upon completion of the 12-week program, using Likert scale questions and optional free-text comment space, targeting each aspect of the exercise intervention: virtual delivery, 1:1 coaching sessions, the exercises included, and use of the Garmin activity tracker. Participants were also asked open-ended items on what they liked or did not like about the program, what they would change, and if they would have preferred an in-person program. Finally, they were asked if they planned to continue exercising even though the exercise intervention had ended. For the main endpoint, we used the question, "how satisfied were you with the exercise intervention overall?" With a Likert scale of 1–5, with 1 being very unsatisfied and 5 being very satisfied. The control group completed an exit questionnaire upon completion of the study. They were asked to rate the following using the same 5-point Likert scale: overall experience participating in the study, satisfaction with the screening and scheduling process and satisfaction with the enrollment visit. If a low rating was given, they were asked to comment on why they were dissatisfied. They were also asked to comment on what they did or did not like about the study and whether they would participate in a similar study again in the future. In addition, we elected to collect post-hoc process information from intervention sessions along with informal qualitative feedback from the health coach to better understand reasons for poor retention and adherence.

2.4.3. Mood, anxiety and stress

Anxiety was measured using the Generalized Anxiety Disorders-7 (GAD-7), and depression using the Neurological Disorders Depression Inventory – Epilepsy (NDDI-E). These are brief and well-validated instruments used clinically in the epilepsy population [36,37]. The items were completed by self-report at baseline and again at the end of the 12-week intervention period. Scores of ≥ 10 on the GAD-7 were considered a positive anxiety screen and scores ≥ 14 on the NDDI-E were considered a positive depression screen [36–38].

Stress was assessed via the Perceived Stress Scale (PSS), a ten-question scale assessing thoughts and feelings of stress over the past month. Individual scores can range from 0 to 40 with higher scores indicating higher perceived stress [39]. This was also completed at baseline and again at the end of the 12-week intervention period.

2.4.4. Social cognitive theory constructs

Exercise goal setting was measured via the Exercise Goal Setting scale (EGS), a 14-item self-report that assess an individual's ability to independently set exercise goals and plan exercise activities [40]. The EGS is measured on a 5-point Likert scale, ranging from 1 (does not describe me) to 5 (describes completely). Higher scores on this measure are indicative of a higher ability to set exercise-related goals and develop an exercise regimen.

Exercise self-efficacy was measured via the Exercise Self Efficacy Scale (EXSE), a six-item scale that assesses individuals' beliefs in their ability to exercise at a moderate intensity three times per week for 30+ minutes per session in the future [41]. Items are answered using a 10-point Likert scale ranging from "not at all confident" to "very confident." Scores range from 0–100 with higher scores indicating higher self-efficacy.

Outcome expectations were measured using the Multidimensional Outcome Expectations for Exercise Scale (MOEES) [42]. This self-report survey includes 15 item to assess 3 related domains of outcome expectations: physical, self-evaluation, and social. Statements are rated on a Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). Higher score indicates higher expectation for outcome of exercise.

2.5. Statistical analysis

Descriptive statistics, including mean (SD) for continuous items and n (%) for count items, was used to characterize key characteristics about the sample. Descriptive statistics were used to explore feasibility and acceptability measures and generate tables and figures in Microsoft Excel software. Python was used to summarize data from Garmin data downloads. Given the low number of study completers, between group comparisons of exploratory pre- and post- outcomes were not performed.

3. Results

3.1. Recruitment

625 charts were reviewed for eligibility, with 262 meeting criteria for preliminary eligibility. Of those, 10 completed enrollment, and 7 completed randomization (Fig. 3), yielding a total recruitment proportion of 1.6 % of the population considered, and 3.8 % recruitment yield of those identified as preliminarily eligible by chart review. Of those who were preliminarily eligible by chart review and able to be reached, 61.9 % declined to proceed with screening, citing reasons such as not interested in research (34.3 %), a lack of transportation (28.6 %), and do not have time (18.6 %).

3.2. Participants

Enrolled participants were 60 % female with mean age 34.7 years (range 24–47 years old) (Table 1). Seven of the ten enrolled participants reported comorbid mental health disorders (anxiety, depression, bipolar disorder, and/or obsessive–compulsive disorder) at enrollment. Three scored positive for active symptoms of anxiety on the GAD-7 and three for active symptoms of depression on the NDDI-E (with four total scoring positive for either anxiety or depression symptoms). Of those with focal epilepsy, two had temporal localization, two had frontal, and one had unknown localization. Five participants had a vagal nerve stimulator (VNS), but one was turned off. One participant had a responsive neural stimulation device (RNS).

3.3. Retention

Two participants dropped out after enrollment but prior to randomization (during the baseline period); one because the watch band caused skin irritation (even after replacing with a different band material) and another did not give a reason. A third enrolled participant broke her leg in an unrelated mechanical fall during the baseline period and was removed by the primary investigator (PI) prior to

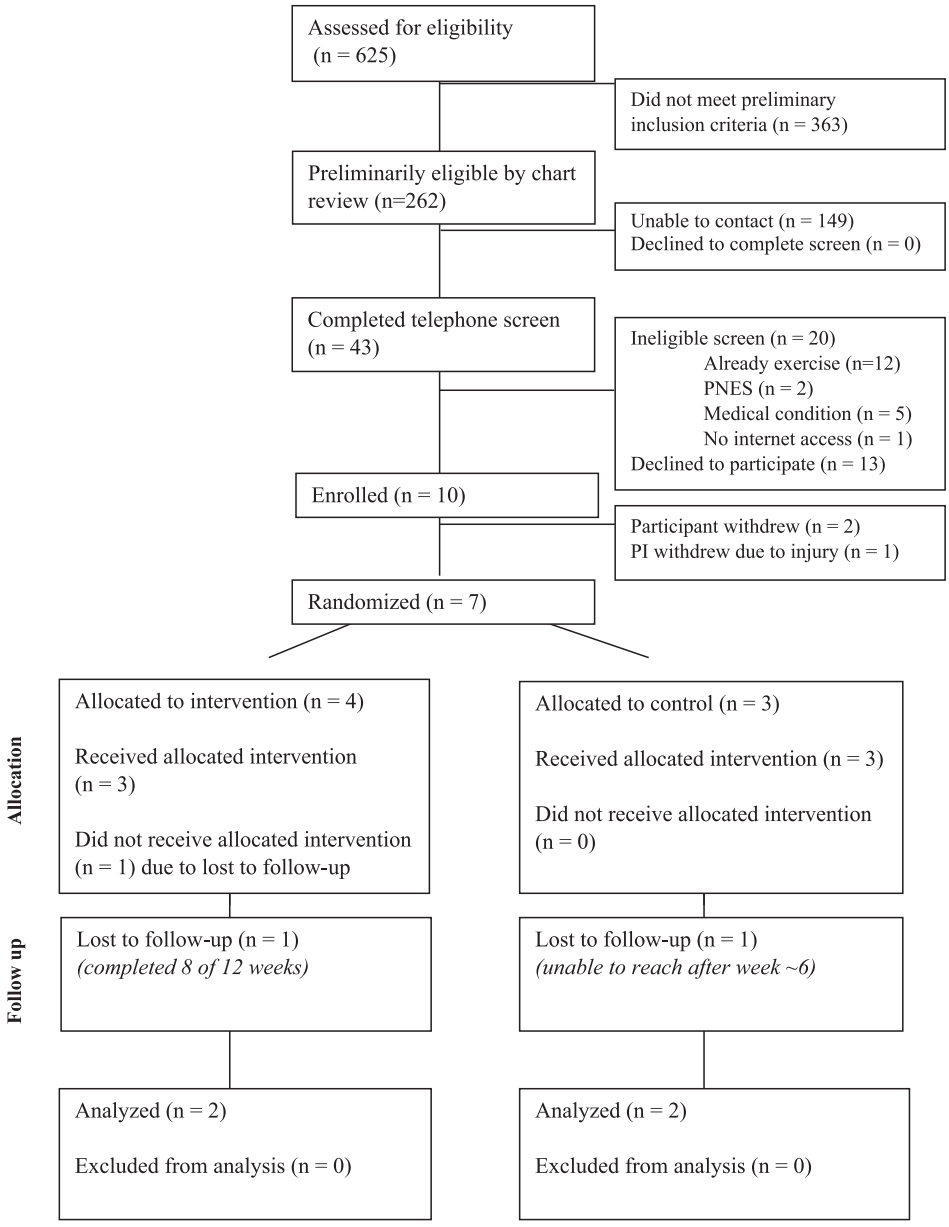


Fig. 3. CONSORT diagram of participants.

randomization. Of the seven randomized participants, three were lost to follow-up prior to completing their post-assessment visit (two from the intervention group and one from control), yielding a retention of 40 % of those consented and 57.1 % of those randomized.

We explored possible mental health-related moderators of retention by plotting baseline anxiety (GAD-7), depression (NDDI-E), and stress (PSS) between study completers and non-completers (Fig. 4), which showed that study non-completers generally had higher scores on anxiety, depression, and stress scales. Only one participant out the four who screened positive for either active anxiety or depression symptoms completed the study, and that participant's score for anxiety was just over the cutoff with a score of 10 and depression screen was negative.

3.4. Uptake

Of the four participants allocated to the intervention group, only two (50 %) completed all their intervention visits and the follow-up assessment. One participant was randomized to the intervention group but then lost to follow-up and was never successfully contacted to start the intervention program, though they continued to wear their Garmin activity tracker. Another participant completed 8 of the 12 weekly intervention sessions and then was lost to follow-up. Uptake did not meet the a priori goal in any of the three participants who received the intervention, and there appeared to be no substantial improvement in physical activity, as measured by minutes of moderate to vigorous intensity physical activity or steps per day, in any participants (Figs. 5–6). We also explored baseline scores on measures of social cognitive theory constructs as possible moderators of physical activity and found these were similar between groups, though the exercise group showed higher average scores on exercise self-efficacy (EXSE), though this did not result in any increased uptake of physical activity behaviors in the exercise group compared to the control group.

Given the poor uptake of assigned exercise goals, the interventionist was informally interviewed post-hoc as a method of feedback on the program. Anecdotally, common challenges encountered included perceived social isolation, frequent fatigue, and depression. Another common barrier was a general hesitation to engage in movement. This was potentially related to the deep-rooted fear of exercise inducing a

Table 1
Enrolled participant demographics (n = 10).

Characteristic	n (%) or mean ± SD
Age; mean ± SD	34 ± 7.7
Sex; n (%)	
Female	6 (60)
Race; n (%)	
White or Caucasian	8 (80)
American Indian or Alaska Native	0
Asian	0
Black or African American	2 (20)
Other	0
Ethnicity; n (%)	
Hispanic or Latino	0
Employment	
Full time	4 (40)
Part time	1(10)
Disability	5 (50)
Body Mass Index (BMI); mean ± SD	34.2 ± 8.0
Monthly seizure frequency; mean ± SD	8.4 ± 11.6
Seizure type; n (%)	
Focal	5 (50)
Generalized	4 (40)
Unknown onset	1 (10)
Duration of epilepsy (years) mean ± SD	20.1 ± 11.9
Number of Anti-seizure medications	
One	1 (10)
Two	6 (60)
Three +	3 (30)
Positive anxiety screen (GAD-7)	3 (30)
Positive depression screen (NDDI-E)	3 (30)

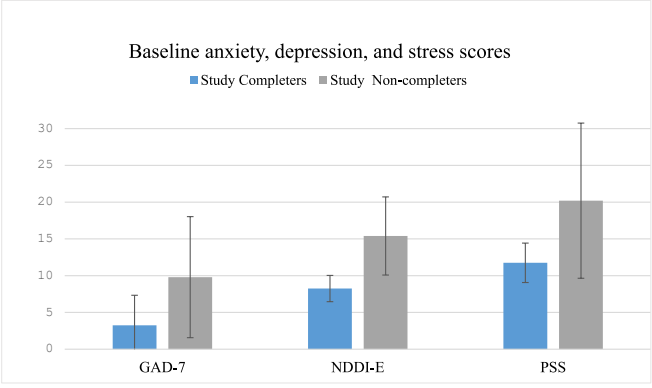


Fig. 4. Baseline scores on anxiety (GAD-7), depression (NDDI-E) and stress (PSS) scales for those who completed the study ("completers") compared to those who did not (non-completers) for all enrolled participants. Error bars represent standard deviation.

seizure or making symptoms of epilepsy worse [15]. This theory is supported by the fact that some participants were resistant to meeting their goals when set as an amount of time in a certain intensity. To combat this, the interventionist also provided goals in the form of a daily step target, which could be achieved at any intensity, which did help some participants come closer to their target.

3.5. Acceptability

Only one participant (001) out of the two who completed the intervention elected to fill out the exercise satisfaction questionnaire. They reported 4/5 satisfaction with the exercise intervention overall and 5/5 satisfaction with the 1:1 coaching, the actual exercises included in the program, and the use of the Garmin activity tracker. They reported "nothing" for what they did not like about the program and that "everything was very helpful." Both participants who completed the control group filled out the exit questionnaire, both reporting scores of 5/5 for overall experience, screening and scheduling process, enrollment visit, and study staff. Both responded "yes" they would participate again if given the option.

4. Lessons learned discussion

The present trial was conducted as a preparatory-phase study within MOST, recognizing the nascency of activity promotion of PWE. Three key related lessons learned emerged. First, we found low appeal of an exercise intervention in our population of DRE as exemplified by very low recruitment response. Second, we found poor study retention with high loss to follow-up, which may relate again to low appeal, compounded by comorbid mental health struggles. Lastly, activity uptake was poor even in those who completed the study, which may again relate to low appeal, mental health struggles, and fear of seizures with exercise.

4.1. Recruitment and retention

A major take-away from this preparatory phase pilot study is that this population with DRE is difficult to recruit from. One reason is that many participants with this large of a seizure burden are non-ambulatory, non-verbal, or otherwise physically or mentally limited in their ability to perform traditional exercise. However, even after excluding participants with these limitations, our recruitment was only 3.8 %. We had many potentially eligible subjects who declined to complete the telephone screen. This could have been partially related to the COVID-19 pandemic, the way in which the program advertised/described by staff, distrust of research, or seasonal timing. Only one other exercise trial has attempted to recruit patients with DRE and a sufficiently high seizure frequency, which also saw similar recruitment challenges with only 28 participants randomized out of a target sample size of 158 [43]. We suspect that recruitment issues for an exercise trial in a population with DRE may be due to the fact that exercise, particularly at high intensities, is inherently unappealing due to kinesophobia, or the fear that exercise will provoke a seizure, a well-documented barrier to exercise in PWE [14–16,44]. In contrast to our study, retention was better in the above mentioned exercise trial in DRE (22/28 completed, 78.5 %) wherein an ergonomic stationary bicycle was sent to the participant's home [43]. This free and easy access to an in-home aerobic exercise machine and the ability to exercise in the safety of their own home by rate of perceived exertion instead of a prescribed heart rate intensity, may have mitigated some of the fear and stigma around exercise for this population.

Our retention goals also did not meet our a priori determination of successful retention. While some participants had unexpected and unrelated circumstances that led them to leave the study, the major reason for non-completion was being lost to follow-up. We suspect that much of this may be related to a mismatch between the requirements of our program and the motivation and readiness of the participants who enrolled, as we employed extensive outreach and engagement efforts by study staff including frequent phone calls, emails, and reminders to both participants and their listed secondary contacts. It is known that adherence to medical therapy such as anti-seizure medication can be challenge in the epilepsy population, with rates of non-adherence up to 50 % [45,46], again reinforcing the issue that very tailored and novel strategies are likely needed to help improve follow-up and engagement in people with DRE.

As noted above, it was common for those who enrolled to have symptoms of depression and/or anxiety that presented challenging barriers to this structured exercise intervention. Indeed, we found that scores on depression, anxiety, and stress screeners were much higher among non-completers compared to completers. We also allowed for caregivers to engage in enrollment procedures, though the intervention was delivered on a 1:1 basis to the PWE. For future implementations of a remote exercise intervention, ensuring readiness and engagement of the

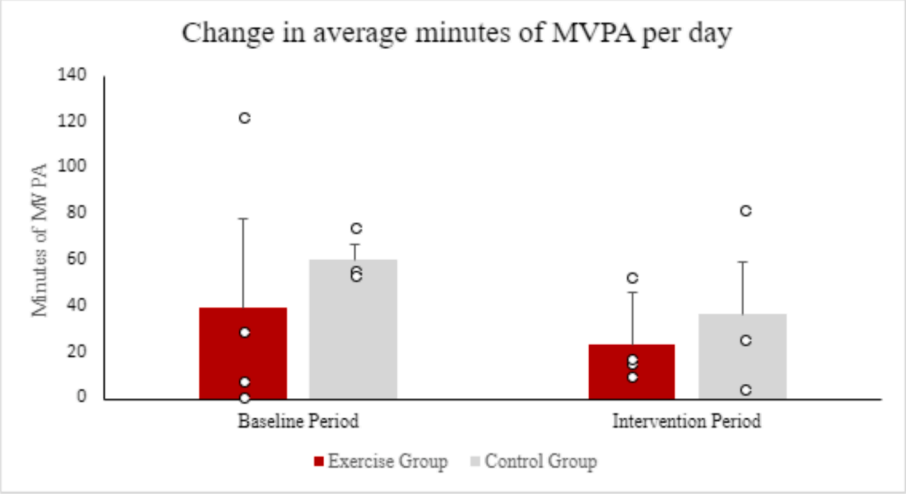


Fig. 5. Randomized participants (n = 7) change in average daily minutes spent in moderate-to-vigorous physical activity (MVPA) when comparing the last week of the baseline period to the last week of the intervention period. Error bars represent standard deviation and dots represent the individual measurements.

participant (and not just the caregiver) will be important. A run-in period where participants must meet certain adherence metrics during the baseline could be used to ensure participants have the capability and motivation to meet program demands. Acknowledging, however, that many PWE will therefore not be eligible for this variety of exercise intervention, it is also worth exploring the benefit of pairing activity promotion with psychotherapy targeting depression or anxiety as needed, given high rates of these mental health conditions among PWE [47,48].

For those interested in providing the potentially potent medicine of activity to PWE with active seizures, additional focused and iterative research on effective recruitment and retention, including education on the safety of exercise for prospective participants and their families, is required.

4.2. Intervention uptake

The health coach noted several barriers during the pilot. One barrier was mental health challenges, which tended to impact motivation and energy levels. As noted above, simply excluding PWE with comorbid mental health disorders from future exercise trials is not a reasonable solution as not only is this a highly prevalent condition in PWE, but this population is likely to benefit the most from increasing their physical activity, given the known benefits of activity on mood, well-being, and quality of life [49]. Instead, future trials should adapt the intervention to accommodate this barrier, such as including more cognitive behavioral reframing in the coaching sessions, adapting the intervention to have an even more gradual progression to help build confidence and momentum early on, or perhaps even including a concurrent mental health component to the intervention as noted above.

Another major barrier was the hesitation to engage in activity. Notably, this barrier is not unique to the epilepsy population. In all people, there is considerable heterogeneity in affective responses to exercise, and many do not experience exercise as a positive affective endeavor. These feelings of displeasure drive adherence more than the cognitive decision to want to exercise [50,51]. In a population of PWE with higher prevalence of comorbid depression, fear of negative health consequences with exercise, and possibly even medication side effects that make participation in structured exercise more difficult, solo exercise may simply present too many barriers and too little return to drive even short term participation. Future studies may benefit from a group format or from caregiver involvement in the exercise program as a form of social support.

By contrast, the health coach noted several strategies that improved activity participation. These included offering flexibility by adding the option of a step goal, choosing intrinsically pleasant activities (which ranged from mowing lawn to swimming to kick boxing class), and being able to appreciate small benefits such as liking the way they feel after exercise or noticing it is easier to breathe. While flexibility and accommodation to the participant's unique needs and lifestyle was seen as a facilitator of engagement in our very small sample, it is possible that providing more structure, such as in the form of guided exercise multiple times per week could benefit uptake and adherence for others. Indeed, this reflects core tenets of behavioral psychology which includes appealing to intrinsic motivation—which varies by person—and supporting autonomy [27].

4.3. Acceptability

Both intervention and control group participants who completed the study reported high satisfaction with the study, including the exercise intervention, the 1:1 coaching, and study operation. This, however, reflects only the opinions of those who completed the study and would be expected to be lower for those who discontinued, but those who dropped out or were lost to follow-up did not complete the acceptability questionnaires. Thus, our future studies will focus on recording more frequent, real-time feedback on all participants during all stages of the study.

4.4. Limitations

This pilot feasibility study has several limitations, the most prominent being small sample size, which limits the ability to interpret any pre-post intervention change, but provided valuable information on recruitment, retention, and uptake to guide future investigations. Being a single center study focusing exclusively on the population with DRE limits generalizability even further. In addition, there are limitations in using a commercial physical activity monitor such as the Garmin Forerunner 45 used in this study: participants were given a standard user profile (including a standard height, weight, age, and sex) to enhance privacy and this likely affected how well the Garmin device quantifies moderate and vigorous intensity time. In addition, the Garmin algorithm requires a 10-minute duration of MVPA in order to count the activity, thereby missing MVPA durations < 10 min despite the updated Physical Activity Guidelines for Americans, which highlight that bouts of any duration positively affect health [25]. Lastly, leveraging the Garmin to collect activity data requires the participant to wear, charge, and maintain the device, potentially missing physical activity during non-

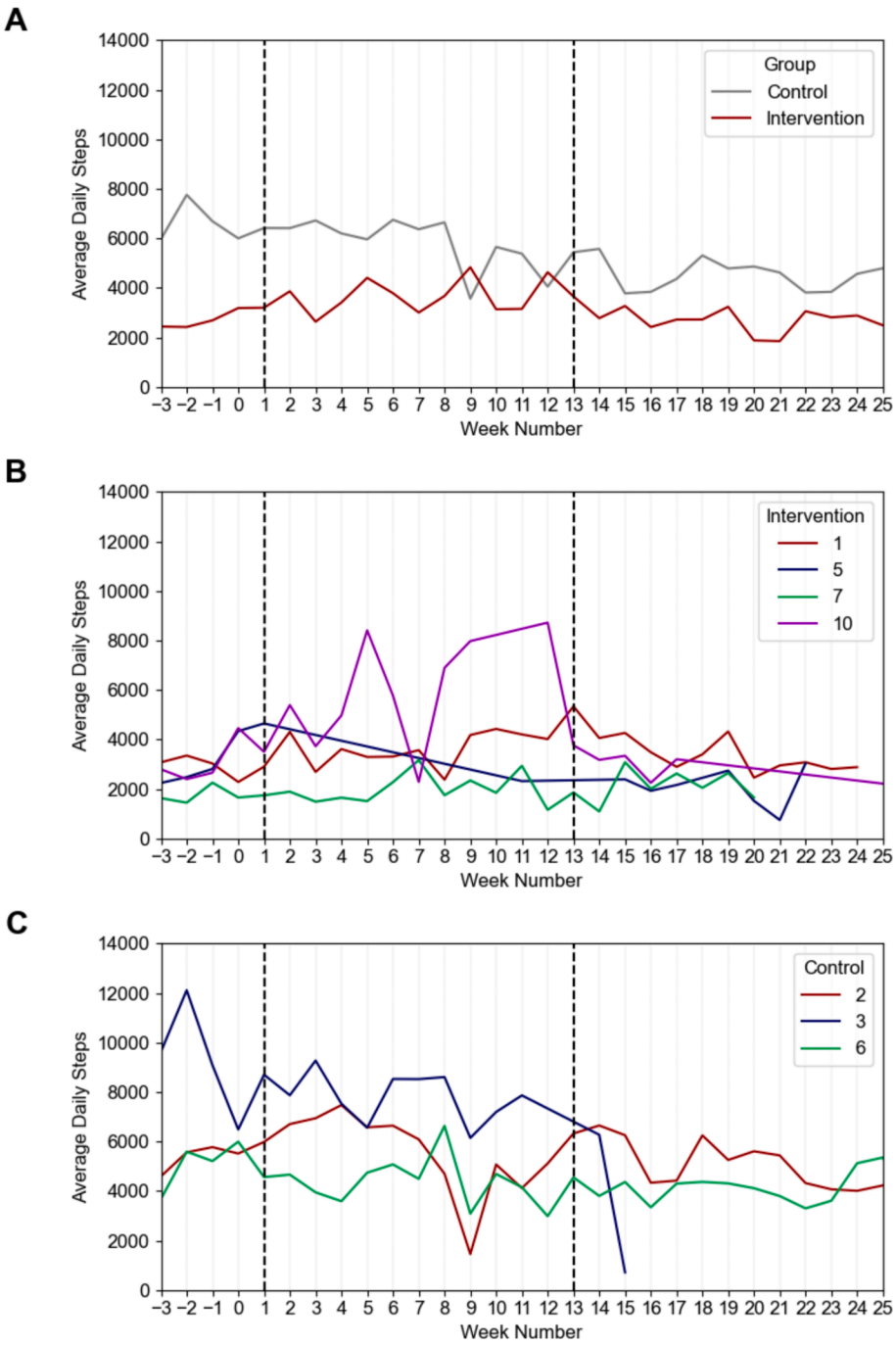


Fig. 6. A.) Group level average daily steps per week B.) Individual level average daily steps per week for the intervention group (participant numbers 1,2,7, and 10) C.) Individual level average daily steps per week for the control group (participant numbers 2, 3, and 6). Vertical dashed bars delineate the baseline (weeks −3–0), intervention (weeks 1–12), and maintenance (weeks 13–25) periods.

wear times or due to technical errors. Relatedly, Garmin devices do not allow for detecting of wear time, requiring proxies for wear time (e.g., a minimum number of daily steps) for which there are no published guidelines. Thus, we cannot be sure that days with low levels of activity are driven by behavior or non-wear.

4.5. Future directions

PWE stand to benefit tremendously from the medicine of physical activity, but as illustrated by the results of this study, it is vital that a careful and iterative approach is taken to crafting impactful and sustainable activity promotion programming for these individuals. PWE face tremendous barriers to participation in structured exercise, such as limited transportation, reliance on caregivers, cognitive impairment, comorbid mood disorders, and high degrees of kinesiphobia. It is notable that structured exercise interventions for individuals *without* such potent barriers have a modest impact on increasing and maintaining physical activity, with median adherence to physical activity behaviors in the general population around 50–60 % and average long-term gains in weekly energy expenditure around 11 % [52–54]. Sufficient physical activity to achieve maximal health benefits in most domains is 150 min per week of moderate to vigorous physical activity. Recent evidence shows that these benefits can be obtained by being broken up throughout the day in bouts of any duration and that even reducing

sedentary time has significant health benefits [49]. Moreover, numerous studies have shown that significant support is needed from a psychological perspective to achieve physical activity behavior change in any population, such as goal-setting, emphasis on enjoyment, and development of self-efficacy [55], and use of a tailored approach [54]. For these reasons, and given the challenges we report herein related to recruitment and retention of PWE in exercise, a traditional exercise intervention for PWE may not be the best approach to activity promotion. This consideration aligns with increasingly accepted views that 1) many people have negative implicit associations with exercise behaviors, which affect their response to both study advertising and daily exercise goals [50]; 2) general health improvements are associated with total volume of weekly activity, not the domain in which it was achieved nor the duration of the activity bout [25,49]; 3) traditional exercise interventions are shown to be minimally effective at increasing physical activity behaviors long-term, even in populations without such significant additional barriers [56]; and 4) the "medicine" of physical activity must be matched to the health outcome of interest. This highlights a very important area of research: how should you approach the medicine of movement in a sample with DRE? Our results suggest we are in sore need for additional preparatory research to gain a better understanding of tolerable and potentially effective approaches to activity promotion—methods that should be further refined in future optimization research. The results of this study point to several refinements for future work: (1) adopt a more diverse approach to activity promotion; (2) conduct the trial in a more socially rich environment to provide greater social support, and (3) consider the use of caregiving dyads and mental health support to better meet the needs of the patient and (4) improve marketing and education for the epilepsy population regarding the safety and benefits of physical activity.

5. Conclusion

There is a paucity of investigation into the best methods to address physical inactivity in PWE. For these reasons and because of the unique challenges in this population, we must work carefully and iteratively in these preparation phase studies and publish our lessons learned along the way [57]. We believe this early experience attempting to intervene on exercise behavior in PWE sets the stage for a large body of exciting future work exploring how to maximize interest in, and uptake of, diverse activity behaviors among PWE, alongside investigating which aspects of activity prescription (e.g., both dose and psychosocial factors such as managing mental health barriers, kinesiphobia, and caregiver needs) are required to maximize health benefits in this population.

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Statement of ethics

All sources of funding and conflicts of interest have been disclosed above. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

CRediT authorship contribution statement

Halley B. Alexander: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Heidi M. Munger Clary:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Hossam A. Shaltout:** Writing – review & editing, Supervision, Software, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Nathan B. Fountain:** Writing – review & editing, Supervision, Methodology. **Pamela Duncan:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Data curation, Conceptualization. **Peter Brubaker:** Writing – review & editing, Resources, Methodology, Funding acquisition, Data curation, Conceptualization. **Jason Fanning:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

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Hossam Shaltout has nothing to declare.

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Pamela Duncan has nothing to declare.

Peter Brubaker has nothing to declare.

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