BMJ
open

Post-training results from a randomized controlled trial to improve cognitive functioning in older adults: the Iowa Healthy and Active Minds Study

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Post-training results from a randomized controlled trial to improve cognitive

functioning in older adults:the Iowa Healthy and Active Minds Study

Fredric D. Wolinsky
Mark W. Vander Weg
M. Bryant Howren
Michael P. Jones
Rene Martin
Tana M. Luger
Kevin Duff
Christopher Goerdt
Steven Wolfe
Megan M. Dotson

Running Head: Post-training results from the IHAMS trial

1

Abstract

Objectives:The Iowa Healthy and Active Minds Study (IHAMS) is a four-arm, randomized controlled trial of a visual processing speed training program known as *Road Tour*. This article reports the post-training (6-8 weeks after randomization) results for the primary outcome.

Design:Within two age strata (50-64 vs. $\geq$ 65), 681 men and women attending general internal and family medicine clinics were randomized to four treatment groups: (1) a supervised, on-site,standard(10-hour) dose of*Road Tour* training;(2) a supervised, on-site,standard dose of *Road Tour* training with subsequent booster training; (3) a supervised, on-site, standard dose of attention control training using computerized crossword puzzles; and, (4) a self-administered, at-home, standard dose of*Road Tour* training. The primary outcome was the Useful Field of View (UFOV) PC mouse version. Intent-to-treat multiple logistic regression analyses of post-training improvements $\geq$ 100 milliseconds (0.55 standard deviations) in the UFOV test was conducted among the 616 participants (90.4%) with complete baseline and post-training data.

Results: In pooled analyses of both age strata, random assignment to any *Road Tour* training group vs. the attention control group was statistically significant (p < .001), with an odds ratio (adjusted for the UFOV test at randomization)of 4.85 (CI$_{95\%}$ = 2.60 – 9.05; AUC = 0.92). Similarresults were obtained for each *Road Tour* group and within each age-stratum.

Conclusion:A 10-hour doseof*Road Tour*training resulted in clinically and statistically significant post-training improvements in visual processing speed. *Road Tour* appeared to be equally effective regardless of whether it wasadministered under laboratory

2

supervision or self-administered in the patient's home. *Road Tour* was also equally

effective among participants in both age strata (50-64 vs. $\geq$ 65).

<u>Clinical Trial Registration Number</u>: NCT01165463.

Article Summary

Article Focus:

- Becauseage-related declines in cognitive functioning are a part of the normal aging process, there is a pressing need to identify efficient and effective training interventions that improve cognitive functioning in older adults.

- This article reports the post-training results of the IHAMS four-arm RCT of three modes (supervised on-site without booster training, supervised on-site with booster training, and self-administered at-home use) of delivering a computerized visual speed of processing intervention vs. an attention control group (supervised on-site computerized crossword puzzles without boostertraining).

Key Messages:

- IHAMS is the first RCT to evaluate the efficacy and effectiveness of *Road Tour*, a second-generation computerized visual speed of processing intervention.

- The results demonstrate clinically and statistically significant post-training improvements in visual processing speedregardless of whether it was administered under laboratory supervision or self-administered in the patient's home, and for both age strata (50-64 vs. $\geq$ 65).

Strengths and Limitations of This Study:

- Strengths: this study design is a four-arm RCT that uses a large sample of men and women $\geq$50 years old and overcomes the important limitations of a previous multi-site trial.

4

- Limitations: although the sample is large, it was drawn from just one familycare center in which minorities are underrepresented, and data on the primary outcome are currently available only at randomization and after initial training (6-8 weeks post-randomization).

Introduction

It is well established that age-related cognitive decline is a common, normal part of the aging process that occursacross many cognitive functions including memory, orientation, attention, abstract thinking, and perception [1-4]. These age-related cognitive changes can be viewed as the result of physical, behavioral, and environmental changes that combine to promote negative brain plasticity and degradations in functioning [5]. Fortunately, this capacity for physical and functional brain change across the lifespan is bi-directional [5,6].Indeed, just as brain plasticity can lead towards degradation in cognitive functioning with age, this same plasticity process can also be used to strengthen cognitive abilities [7-9]. This is especially important given recent evidence demonstrating that these age-related declines commence as early as age 28 and then continue in a linear fashion throughout the remainder of the life course [9].

Many training programs have been developed to help mitigate these age-related cognitive functioning declines. Although the gains associated with most earlier cognitive training interventions appeared to be highly task-, and context-specific, more recent developments have demonstrated that improving the coordination of executive skills can transfer beyond the testing environment [7]. These often involvecomplex video games, task-switching paradigms, or divided attention tasks because these training platforms provide a carefully controlled and well-structured environment. Someof these successful interventionshave focused on improving visual information processing

6

speed, which is not surprising given the considerable evidence that supports the role of processing speed in age-related cognitive decline [10-12].

Perhaps the most extensively evaluatedinterventionthat targets improving visual processing speed is that developed by Ball and Roenker[4,13,14]. Their program trains users to improve the speed and accuracy with which they identify and locate visual information using a divided attention format. Over time, the difficulty and complexity of each task is systematically increased as users attain specified performance criteria. Manipulations to increase difficulty include decreasing visual stimuli duration, adding visual or auditory distracters, increasing similarity between target and distracter stimuli, and presenting visual targets over a broader spatial expanse. The basic tasks, however, are always the same—central discrimination and peripheral target location. Substantial evidence from the USA NIH-funded multi-site RCT known as ACTIVE (Advanced Cognitive Training for Vital Elderly) has shown the efficacy of Ball and Roenker's visual processing speed intervention on both immediate and distal cognitive functioning, as well ason subsequent health outcomes [15-24].

Posit Science Corporation (San Francisco, California, USA) recently acquired the rights to Ball and Roenker'svisual speed of processing training program [4,13,14]. While all of the original tasks were maintained, the delivery platform was modified to be user-friendly and self-administered. Gaming elements were also added to improve user engagement and enhance compliance. The resulting second-generation computerized visual speed of processing training program is known as *Road Tour*, and is commercially available as part of the*Insight*^{tm} visual processing speedsuite, or as part of the*DriveSharp*^{tm} driving suite (http://www.positscience.com/our-products).

7

We designed the Iowa Healthy and Active Minds Study (IHAMS) to evaluate the efficacy and effectiveness of *Road Tour*. IHAMS is a four-group parallel RCT(NCT01165463) whose protocol has been described in detail elsewhere [25]. In this article we report on the post-training (6-8 weeks post-randomization) results for the primary outcome. Because no standard booster training occurred by this time, and because supplemental training beyond 10 hours in the at-home group should have been minimal, we hypothesize that participants randomized to *Road Tour* training (Groups 1, 2, and 4) should have significantly and similarly greater improvements in visual processing speed immediately after training than the attention control group (Group 3).

Methods and Analysis

Overview.Figure 1 shows the IHAMS study design and participant recruitment results. IHAMS used a 3:3:4:4 allocation ratio and block randomization separately within two age-strata (50-64 vs.$\geq$ 65). Participants were randomized to one of the following groups: (1) 10 hours (over the first 5-6 weeks)ofsupervised on-site training using *Road Tour*(Group 1), (2) 10 hours of supervised on-site training using *Road Tour* plus 4 hours of booster trainingat 11 months post-randomization (Group 2), (3) 10 hours of supervised on-site attention control (Group 3) using computerized crossword puzzles (*Boatload of Crosswords*, Boatload Puzzles, LLC, Yorktown Heights, New York, USA), or (4) self-administered at-home training using *Road Tour* for 10 hours or more (Group 4). Enrollment of the 681 participants occurred from April toNovember 2010, with 154 randomized to Group 1, 148 to Group 2,188 to Group 3,and 191 to Group 4.Post-training assessments occurred at 6-8 weeks post-randomization, and complete baseline and post-training data were obtained for 616 participants (90.5%). One-year post-

randomization assessments are scheduled to be completed by late November 2011. IHAMS was sized to provide $\geq$ 80% power to detect an effect size of 0.25 in the primary outcome at one-year post-randomization with alpha = 0.05.

Sampling Frame.We includedall patients attending either the general internal or family medicine clinics of the University of Iowa'sFamily Care Center (FCC) in the IHAMS sampling frame. The electronic medical recordwas used for initially selecting potentially eligible participants. The initial inclusion criteriawere: (1) age $\geq$ 50 years old, (2) $\geq$ 2 visits to a primary care physician in the FCCin the past year, and (3) the absence ofdiagnostic codes for Alzheimer's or Picks' disease, arteriosclerotic dementia, other senile or pre-senile dementia, dementia due to alcohol or drugs, amnestic syndrome, or dementia due to other organic conditions. A total of 5,743 potentially eligible patients were identified. Weekly random replicates of 100-250 of them were sent a letter describing the study and asking them to telephone the project office and indicate whether or not they were interested in participating.

Telephone Screening.We attempted to further screen all potentially eligible patients, but could not reach 1,627. Of the remainder, 2,079 declined to participate. We conducted brief screening interviewsto identify potential participants who met any of the following exclusion criteria: (1) significant cognitive impairment based on $\geq$3 errors on a 10-item mental status exam [26], (2) significant self-reported uncorrected visual acuity problems, (3) not having a personal computerwith a CD-ROM in the home, (4) not having internet access, and (5) having previously used a computerized program for improving cognitive function. This resulted in the exclusion of 1,356 potential participants.

9

Informed Consent and Baseline Interviews.After completing the screening interview, eligible patients were scheduled for a two-hour visitto our laboratory where written informed consent was obtained. Then, the 681 enrollees were administered their baseline (randomization) interviews by trained research assistants using computer-assisted interviewing protocols. Immediately afterwards each participant was randomized to one of the four study groups.

Randomization Procedure. The study biostatistician (MPJ) determined the order of assignments using a computer-generated list of random numbers anda 3:3:4:4 ratio based on *a priori* power calculations. Block randomization was used to maintain balance on two age-strata (50-64 and $\geq$ 65). Block sizes of 4, 8, and 12wererandomly varied. The assignment for each participant's ID number was recorded on a participant letter and then sealed in an opaque envelope with only the ID number visible. Two age-strata specific boxes containing the assignment envelopes were stored in a locked cabinet in the Project Coordinator's office. The Project Coordinator (MMD) had the responsibility of unsealing the envelope (from the appropriate age-stratum box) and revealing each participant's group assignment.

Cognitive Processing Speed Outcomes. The six neuropsychological assessments are: (1) the UFOV PC mouse version [27]; (2) the Symbol Digit Modalities Test (SDMT) [28]; (3) the Trail Making A and B Tests (TMT) [29]; (4) the Controlled Oral Word Association Test (COWAT) [30]; (5) the Digit Vigilance Test (DVT) [31]; and, (6) the Stroop Color and Word Test (Stroop) [32]. The UFOV test is the primary outcome and earlier versions of it have been used in most prior visual speed of processing studies, including ACTIVE. Itwas administered at randomization and post-training (6-8

10

weeks post-baseline), and will be administered at one-year post-randomization. The

UFOV includes three subtests—stimulus identification, divided attention, and selective

attention—each of which is scored from 17-500 milliseconds (ms) reflecting the shortest

exposure time at which the participant could correctly perform each subtest 75% of the

time, with a composite ms outcome score ranging from 51-1500 ms.

The SDMT, TMT, COWAT, DVT, and Stroop tests are secondary outcome

measures, were all administered at randomization, and will be administered at one-year

post-randomization. SDMT captures divided attention and processing speed, and is

based on how many of 110 possible digit-symbol pairs were scored as correct pairs by

the participant in 90 seconds. TMT assesses visual scanning ability, processing speed,

and set-shifting/executive functioning, and is coded as the number of seconds needed

to correctly complete connecting the number and number-letter sets. COWAT assesses

verbal fluency based on the number of unique words beginning with the letter C (or F or

L) generated by the participant during 60 seconds, with a composite score of the

number of correct words used across the three letter trials. DVT assesses sustained

attention and psychomotor speed, is performed by crossing out randomly placed 6's in

59 rows of numbers, and is scored as the error and time totals. The Stroop assesses

processing speed and executive functioning, and is scored as the correct number of

words, colors, and color-words identified in 45 seconds on each subtest.

The *Road Tour* Training Program. *Road Tour's* basic appearance to the useris

shown in Figure 2a. After clicking on the start button to initiate training, Figure 2b is

shown. Here, both the license plate area and the eight circular locations in the near

orbit surrounding it are empty. The empty license plate is then replaced, as in Figure

2c, with the target vehicle, either a car or a truck. Similarly, the eight empty circular

locations surrounding the license plate are then replaced with seven distracter stimuli

(rabbit crossing signs) or the target sign (Route 66). The stimuli (car vs. truck, and

rabbit crossing vs. Route 66 sign) are presented for a specified time and are then

replaced by Figure 2d. The amount of time that Figure 2c remains on the screen before

being replaced by Figure 2d is measured in ms. In Figure 2e, both target vehicles (the

car and truck) are presented in the center of the screen, one of which was previously

shown in Figure 2c as the target. The user first clicks on the correct target vehicle (car

or truck), and then on the circular location where the correct peripheral target (Route 66

sign) appeared (Figure 2f). The goal is to improve cognitive processing speed by

progressively reducing the ms of exposure that Figure 2c remains on the screen with

subsequent correct identification of both the stimuli (car or truck) and target (Route 66)

sign. As the user progresses, three changes occur which further increase task difficulty:

(a) the target visual field expands by progressing outward from the license plate to add

medium and distal orbits, (b) these are accompanied by an increasing number of

distracters to fully populate all three orbits (up to 47), and (c) the vehicle pairs morph

through 9 different stages or pairs to become more similar and thus more difficult to

differentiate.

   Analysis.First, one-way analysis of variance for selected participant

characteristics, training time, and the six neuropsychological outcomes was conducted.

The interrelationships among the six neuropsychological assessments at baseline were

then explored using exploratory factor analysis. To assess the effects of *Road Tour*

training (vs. attention control training) on the primary outcome, we used multiple logistic

regression analysis. Our first model involved the single binary contrast of being randomly assigned to any *Road Tour* training, adjusting for the value at randomization. We then substituted three mutually exclusive binary indicators for the single binary contrast. These three binary indictors reflect whether the participantwas in the on-site speed of processing intervention without boosters, the on-site speed of processing intervention with boosters,or the at-home speed of processing group vs. those in the on-site crossword puzzle (attention control) group as the reference or omitted category. We then estimated both the first and second model separately within each age stratum.

Results

Baseline Group Comparisons.Table1 compares the four treatment groups on selected participant characteristics (including the self-rated health and change in self-rated health from one-year ago items from the SF-36 [33]), amount of training (in minutes) received, and the six neuropsychological tests at randomization. No significant differences were found for any of the participant characteristics. Significant differences were observed, however, on the amount of training received. The attention control group received the most training, while the at-home *Road Tour* training group received the least. This is not surprising given the efforts to schedule the five, two-hour training sessions for all participants in the three on-site training groups. Moreover, on-site *Road Tour* participants were allowed to stop their training once they had completed all 81 of the available exercise sets, which occurred about 5% of the time. Finally, although *Road Tour*directly monitors training in minutes based on actual program usage, participant training in the attention control group was monitored by project staff based on the completion of two-hour training sessions.

13

Significant differences between the groups were also observedfor the SDMT, TMT (A and B), and the word and color sub-tests of the Stroop. In all cases, the attention control group demonstrated the lowest level of performance. These differences, however, were modest in the absolute, although*post-hoc*comparisons using Dunnetttests found 8 of the 15 group level contrasts involving Group 3 (attention control) to be statistically significant. Group 3 had significantly lower performance than (a) Group 1 on the SDMT, (b) Groups 1, 2, and 4 on the TMT-A, (c) Group 1 on the TMT-B, (d) Groups 1 and 4 on the Stroop word subtest, and (e) Group 1 on the Stroop color subtest. Therefore, wewill adjust for these differences in all subsequent analyses by including the value of the outcome measure at randomization.

Factor Structure among the Outcomes.To examine the interrelationships among the six neuropsychological assessments at baseline,exploratory factor analyses were conducted using principal components extraction methods withoblique rotation. As shown in Table 2, three factors were extracted that had eigenvalues $\geq$ 1.00 (4.38, 1.21, and 1.08, respectively). These three factors accounted for 66.7% of the variance among the ten component scores of the neuropsychological assessments and resulted in a simple factor structure (factor loadings <0.500 omitted for clarity; [36,37]). Based on the assessments that loaded on them, Factor 1 reflects processing speed under divided attention, Factor 2 reflects processing speed under sustained attention, and Factor 3 reflects processing speed in the absence of divided or sustained attention. While Factor 2 was orthogonal to (or uncorrelated with) Factors 1 and 3 (r $\leq$ 0.02), Factors 1 and 3 were highly correlated (r = 0.47). These results suggest that any effects found for *Road Tour* on the UFOV test at post-training should, to some

14

extent,transfer to the other assessments, except perhaps for the DVT. Definitive

evidence, however, must await the availability of the one-year post-randomization data.

Post-Training Effects.To assess the hypothesis that random assignment to any of

the *Road Tour* treatment groups should have resulted in significantly greater and similar

post-training improvements (6-8 weeks post-randomization) in visual processing speed

compared to the attention control group, we conducted intent-to-treat analysis using

multiple logistic regression models to predict improvements$\geq$ 100 ms. We chose logistic

regression and thisspecific effect threshold for two reasons. First, the distribution on the

UFOV test at both randomization and 6-8 weeks post-randomization is not normal,in

part due to the left and right censoring on each of thethree UFOV subtest components.

Second, the 100 ms threshold represents a clinically meaningful improvementthat

corresponds to a standard deviation of 0.55.

At post-training, complete data on the UFOV tests were available for 616

participants (90.4%). With these data, we first conducted pooled analyses (i.e., both

age strata) of random assignment to any *Road Tour* training group vs. the attention

control group, adjusting for the UFOV test at randomization. The adjusted odds ratio

(*AOR*) for being randomized to any *Road Tour* training group on achieving a post-

training improvement in the UFOV test $\geq$ 100 mswas 4.85 ($CI_{95\%}$ = 2.60 to 9.05; *p*<

.001). The absolute improvement effect was 12.2% (34.3% of *Road Tour* subjects

improved $\geq$ 100 msvs. 23.1% or attention control subjects). Not surprisingly,

participants with slower UFOV test scores at randomization were more likely to have

achieved post-randomization improvements, reflecting a 1% greater likelihood per

15

ms(AOR = 1.01; $CI_{95\%}$ = 1.01 to 1.02; p< .001). This simple model fit the data

extremely well (*Area Under the Curve* [*AUC*] = 0.92).

To assess the similarity of the three *Road Tour* groups vs. the attention control

group, we then replaced the single binary marker with a set of three indicators for being

in Group 1, Group 2, or Group 4 vs. the attention control group (Group 3). Table 3first

shows these results for the pooled age strata, and then separately for each age stratum.

The pooled analysis indicates that while the three *Road Tour* groups'*AORs* vary from

4.01 to 5.52 (*p*values< .001; *AUC* = 0.92; absolute improvement effects 10.0% to

12.5%), they all fall within the others' confidence intervals, reflectingsimilar effect sizes.

Comparable results were found within age strata, although the model forthe younger

age stratum fit the data slightly better (*AUC* = 0.95 vs. *AUC* = 0.86). Taken together,

these results support our hypothesis for the post-trainingeffects in all respects.

Conclusion

Gradual cognitive decline is nearly universal andis well-recognized as a normal

part of the aging process. According to Salthouse [36], most age-related cognitive

deteriorations are at least partially attributable to declines in information processing

speed, which affects episodic and working memory, verbal fluency, and reasoning

abilities. Previous work, especially the USA NIH-funded multi-site ACTIVE trial has led

to the development of a promising, second-generation computer-based intervention to

improve visual processing speed known as *Road Tour*. We designed IHAMS to assess

the efficacy and effectiveness of *Road Tour*.

IHAMS is an RCT with participants randomized to four groups. Group 1 received

a standard dose of computerized visual processing speed training on-site in our

laboratory. Group 2 also received a standard dose of computerized visual processing speed training on-site, but was invited back to our laboratory for 4 hours of subsequent booster training. Group 3 received an equivalent dose of attention control training using computerized crossword puzzles on-site in our laboratory. Group 4 took the visual processing speed training software home and was instructed to use it on their ownpersonal computer for at least a standard dose. The primary outcome is visual processing speedas measured by the UFOV test.

In this article, we reported on an exploratory factor analysis of the six neuropsychological assessments at randomization, and on an efficacy analysis of the post-training (6-8 weeks post-randomization)data. The exploratory factor analysis indicated that all of the neuropsychological assessments were highly inter-correlated, except for the DVT. This suggests that effects found for *Road Tour* on the UFOV test at post-training should, to some extent, transfer to the secondary outcomes, except perhaps for the DVT. Definitive evidence, however, must await the availability of the one-year post-randomization data. As with prior studies involving an earlier version of the intervention [4,13,14,16,17], the post-training efficacy analysis yielded statistically and clinically significant improvements in visual processing speed associated with random assignment to a 10-hour dose of *Road Tour* training. The results also showed that speed of processing interventions like *Road Tour* can be self-administered in the patient's home and appear equally effective under those circumstances as when used under supervision in a laboratory. Furthermore, these results provided the first solid evidence that visual speed of processing interventions like *Road Tour* are efficacious among 50-64 year olds as well as among those aged 65 years old or older. In future

17

analyses, we will evaluate the impact of the intervention at one-year on all outcomes,

after these data become available.

End Matter

Competing Interests:The *Road Tour* computerized visual speed of processingintervention used in IHAMS is commercially available from Posit Science Corporation (San Francisco, CA, USA).None of the members of the investigative team have any conflicts of interest or commitment involving Posit Science. Specifically, no one on the investigative team will financially profit in any way from the use of *Road Tour*.

Posit Science acquired ownership in October 2007 of Ball and Roenker's [4,13,14] original speed of processing intervention that was used in the multi-site ACTIVE RCT on which FDW was an original co-investigator (at the ACTIVE Indiana University site). In collaboration with Professors Ball and Roenker, Posit Science subsequently developed the second-generation, value-added version of the visual speed of processing intervention known as *Road Tour* and used here in IHAMS. From December 2007 to March 2009, FDW had a limited, part-time consulting arrangement (15 days, total) with Posit Science to support additional analyses of the first five-years of the ACTIVE follow-up data that had not been identified in the original ACTIVE protocols nor funded by the various US NIH grants supporting ACTIVE. This arrangement was

19

approved in advance by the ACTIVE Executive Committee (which included the US NIH project officers), and was sanctioned by the Provost of the University of Iowa.

After terminating this limited, part-time consulting arrangement with Posit Science, FDW applied in April 2009 for, and was awarded in September 2009 the US NIH Challenge Grant known as IHAMS. Posit Science provided the 700 copies of *Road Tour* used in IHAMSat no cost or obligation. Furthermore, in its letter of commitment to IHAMS and the US NIH, Posit Science stated should the results support the efficacy and effectiveness of *Road* Tour, they will"work with agencies at the federal government to make the program available for wide-scale implementation at only a fraction of the current per-user cost."

Ethics Approval: Ethics approval was provided by the University of Iowa Institutional Review Board (IRB-03; IRB protocol number 200908789), initially approved on September 12, 2009, and most recently re-approved on May 18, 2011.

Contributors:FDW is the principal investigator on the study, wrote the original proposal, supervised the trial, conducted all of the analyses, and drafted the manuscript. MWV-W is co-principal investigator on the study, collaborated on the original proposal, co-supervised the trial, and reviewed the analyses reported here as well as the manuscript itself. MBH is a post-doctoral fellow working on the study, trained all of the interviewers, supervised the scoring of the neuropsychological tests, and reviewed the manuscript. MPJ is the study biostatistician, devised the randomization protocol, reviewed all of the analyses, and reviewed the manuscript. RM is a co-investigator on the study, reviewed all of the ethics, consent, and IRB documents, and reviewed the manuscript. TML was a study Research Assistant who assisted with piloting the

interview protocol, conducted randomization interviews, and reviewed the manuscript.

KD is the study neuropsychologist, supervised selection of the neuropsychological tests,

reviewed the psychometric analyses, and reviewed the manuscript. CG is the medical

director of the FCCGeneral Medicine Clinic, participated in subject recruitment, and

reviewed the manuscript. SW is the medical director of the FCC Family Medicine Clinic,

participated in subject recruitment, and reviewed the manuscript. MMD is the Project

Coordinator.

Provenance and Peer Review:IHAMS was not a commissioned study. It was

externally peer reviewed by a panel of Distinguished Editors (ZRG1 RPHB-E 58)

convened by the US NIH to select approximately 200 (from a pool of about 23,000

submitted) Challenge Grant Applications (RC1s) submitted in response to the American

Recovery and Reinvestment Act of 2009.

21

References

1. Birren JE, Woods AM, & Williams MV. Behavioral slowing with age: causes, organization, and consequences of slowing.   Pp. 293–308 in Poon LW (ed), *Aging in the 1980s: psychological issues*. Washington, DC: American Psychological Association, 1980.

2. Edwards JD, Wadley VG, Myers RS, Roenker DL, Cissell GM, & Ball KK. Transfer of a speed of processing intervention to near and far cognitive functions. *Gerontol*, 2002;48:329–340.

3. Madden DJ. Four to ten milliseconds per year: age-related slowing of visual word identification. *J Gerontol: Psych Sci*, 1992;47:P59–P68.

4. Roenker DL, Cissell GM, Ball KK, Wadley VG, & Edwards JD. Speed-of-processing and driving simulator training result in improved driving performance. *Hum Factors*, 2003;45:218–233.

5. Mahncke HW, Bronstone A, & Merzenich MM. Brain plasticity and functional losses in the aged: scientific bases for a novel intervention. *Prog Brain Res*, 2006;157:81-109.

6. Greenwood PM. Functional plasticity in cognitive aging: review and hypothesis. *Neuropsychol*, 2007;21:657-673.

7. Hertzog C, Kramer AF, Wilson RS, &Lindenberger U. Enrichment effects on adult cognitive development: can the functional capacity of older adults be preserved and enhanced? *PsycholSci Pub Interest*, 2008;9:1-65.

8. Salthouse TA. Consequences of age-related cognitive declines. *Ann Rev Psychol*, 2012;63: in press.

22

9. Salthouse TA. When does age-related cognitive decline begin? *Neurobiol Aging*, 2009;30:507-514.

10. Clay OJ, Edwards JD, Ross LA, Okonkwo O, Wadley VG, Roth DL, & Ball KK. Visual function and cognitive speed of processing mediate age-related decline in memory span and fluid intelligence. *J Aging Health*, 2009;21:547-566.

11. Lemke U, &Zimprich D. Longitudinal changes in memory performance and processing speed in old age. *Aging, Neuropsychol, Cog*, 2005;12:57–77.

12. Zimprich DM. Can longitudinal changes in processing speedexplain longitudinal changes in fluid intelligence? *Psychol Aging*, 2002;17:690–695.

13. Ball KK, Edwards JD,& Ross LA. The impact of speed of processing training on cognitive and everyday functions. *J Gerontol: SocSci*, 2007;62B:19-31.

14. Ball KK, Beard BL, Roenker DL, Miller RL, & Griggs DS. Age and visual search: expanding the useful field of view. *J Optic SocAmer*, 1988;5:2210-2219.

15.Jobe JB, Smith DM, Ball KK, Tennstedt SL, Marsiske M, Willis SL, Rebok GW, Morris JN, Helmers KF, Leveck MD, &Kleinman K. ACTIVE: a cognitive intervention trial to promote independence in older adults. *Controlled Clin Trials*, 2001;22:453-479.

16. Ball KK, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, Morris JN, Rebok GW, Smith DM, Tennstedt SL, Unverzagt FW, & Willis SL. Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA*, 2002;288:2271-2281.

17. Willis SL, Tennstedt SL, Marsiske M, Ball KK, Elias J, Mann-Koepke K, Morris JN, Rebok GW, Unverzagt FW, Stoddard A, & Wright E. Long-term effects of

cognitive training on everyday functional outcomes in older adults. *JAMA*, 2006;296:2805-2814.

18. Wolinsky FD, Mahncke HW, Kosinksi M, Unverzagt FW, Smith DM, Jones R, Stoddard A, &Tennstedt SL. The ACTIVE cognitive training trial and predicted medical expenditures. *BMC Health Serv Res*, 2009;9:109:1-9.

19. Wolinsky FD, Unverzagt FW, Smith DM, Jones R, Wright E, &Tennstedt S. The effects of the ACTIVE cognitive training interventions on clinically relevant declines in health-related quality of life. *J Gerontol: SocSci*, 2006;61B:S281-S287.

20. Wolinsky FD, Unverzagt FW, Smith DM, Jones R, Stoddard A, &Tennstedt S. The ACTIVE cognitive training trial and health-related quality of life: protection that lasts for five years. *J Gerontol: Med Sci*, 2006;61A:1324-1329.

21. Wolinsky FD, Vander Weg MW, Martin R, Unverzagt FW, Ball KK, Jones R, &Tennstedt SL. The effect of speed of processing training on depressive symptoms in ACTIVE. *J Gerontol: MedSci*, 2009;64A:468-472.

22. Wolinsky FD, Mahncke HW, Vander Weg MW, Martin R, Unverzagt FW, Ball KK, Jones R, &Tennstedt SL. The ACTIVE cognitive training interventions and the onset of and recovery from suspected clinical depression. *J Gerontol: PsycholSci*, 2009;64B:577-585.

23. Wolinsky FD, MahnckeHW, Vander WegMW, MartinR, UnverzagtFW, BallKK, JonesR, &TennstedtSL. Speed of processing training improves self-rated health in older adults: enduring effects observed in the multi-site ACTIVE study. *IntPsychogeriatr*, 2010;22:470-478.

24

24. Wolinsky FD, Vander WegMW, MartinR, UnverzagtFW, WillisSL, MarsiskeM, RebokGW, MorrisJN, BallKK, &TennstedtSL. Cognitive training improves internal locus of control among older adults. *J Gerontol: SocSci*, 2010;65B:470-478.

25. Wolinsky FD, Vander Weg MW, Howren MB, Jones MP, Martin R, Luger TM, Duff K, Goerdt C, Wolfe S, &Dotson M. Protocol for a randomized controlled trial to improve cognitive functioning in older adults: the Iowa Healthy and Active Minds Study.*BMJ Open*, 2011-000218, in press.

26. Pfeiffer EA. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients.*J Am GeriatrSoc*. 1975;23:433-41.

27. Edwards JD, Vance DE, Wadley VG, Cissel GM, Roenker DL, & Ball KK. Reliability and validity of Useful Field of View test scores as administered by personal computer. *J ClinExperNeuropsychol*, 2005;27:529–543.

28.Smith A. *Symbol digit modality test*. Los Angeles, CA: Western Psychological Services, 1982.

29. Reitan RM,&Wolfson, D.*The Halstead-Reitanneuropsychological test battery: therapy and clinical interpretation*. Tucson, AZ: Neuropsychological Press, 1985.

30.Benton AL, Hamsher K, &Silvan AB. *Multilingual aphasia examination* (3rd Edition). Iowa City, IA: AJA Associates, 1994.

31. Lewis R,&Rennick PM.*Manual for the repeatable cognitive-perceptual-motor battery*. Gross Point, MI: Axon, 1979.

32. Golden CJ. *The Stroopcolor and word test*. Chicago, IL: Stoelting Company, 1978.

25

33. McHorney CA, Ware JE, &Raczek R. The MOS 36-Item Short-Form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*, 1993;31:247-263.

34. DeVellis RF. *Scale development: theory and applications*. Newbury Park, CA: Sage, 1991.

35.Nunnally JC. *Psychometric theory*. New York, NY: McGraw-Hill, 1967.

36. Salthouse TA. The processing-speed theory of adult age differences in cognition.*Psychol Rev*, 1996;103:403-428.

26

Figure 1.IHAMS CONSORT Flow Diagram.
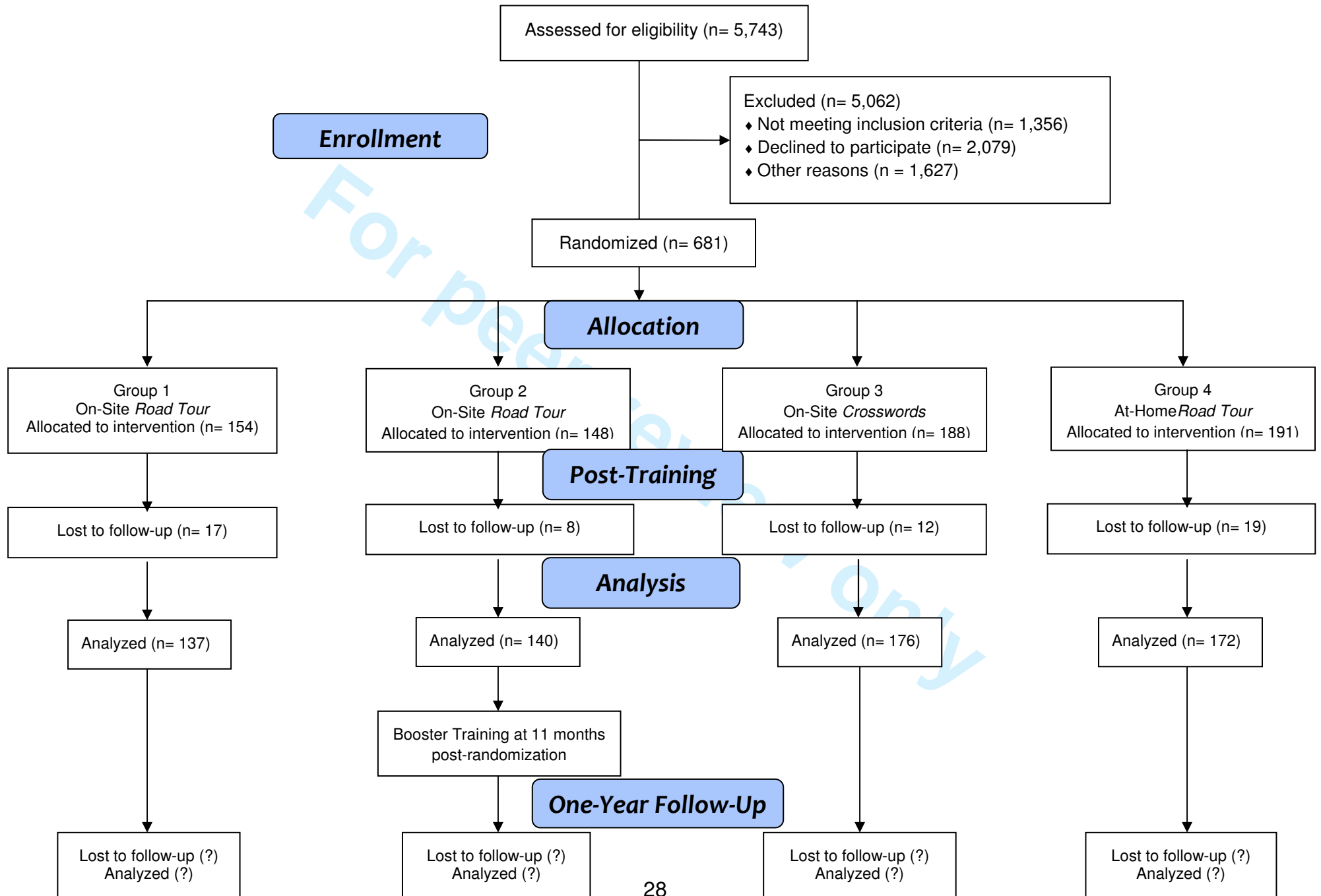
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Figures 2a-f.The Initial *Road Tour* Sequence.

Table 1.Means of Selected Participant Characteristics and the Six Neuropsychological Tests at Randomization by Treatment Group Status, N = 681.

Variable	Overall N=681	Group 1 N=148	Group 2 N=154	Group 3 N=188	Group 4 N=191	*p* value
Personal Characteristics						
Age (years)	61.9	61.4	62.5	61.8	61.9	0.676
Men (%)	37.3	37.2	32.5	42.0	36.7	0.340
Married (%)	69.9	73.0	61.0	73.4	71.2	0.053
Single (%)	11.2	10.1	14.9	8.0	12.0	0.219
Working (%)	54.5	56.8	53.9	50.0	57.6	0.459
Retired (%)	35.5	35.1	36.4	34.2	34.6	0.982
Income $\leq$ \$35K (%)	28.3	24.3	36.4	27.7	25.7	0.079
Income $\geq$ \$75K (%)	46.6	45.3	41.6	47.3	50.8	0.383
Self-Rated Health (5=best 1=worst)	3.8	3.8	3.8	3.7	3.9	0.526
One-Year Change in Self-Rated Health(5=best 1 =worst)	3.2	3.3	3.3	3.2	3.3	0.646
Training Time						
Minutes of Training	469	450	488	535	404	0.001
Neuropsychological Tests						
UFOV Composite (ms)	300.0	282.7	301.2	319.9	292.8	0.277
SDMT (# correct)	50.5	51.8	50.5	48.7	51.1	0.015
Trails A (sec)	41.9	40.9	39.8	45.0	41.2	0.001
Trails B (sec)	66.9	63.8	65.8	71.8	65.2	0.030
COWAT Composite (# words)	42.0	42.4	41.9	40.5	43.2	0.153
DVT Errors (#)	8.1	7.5	9.0	7.9	8.0	0.427
DVT Time (sec)	377.0	369.0	374.8	387.9	374.5	0.190
Stroop Word (#)	70.4	71.2	71.8	68.1	71.1	0.038
Stroop Color (#)	97.8	100.3	96.5	95.3	99.3	0.032
Stroop Color-Word (#)	38.1	38.7	38.0	37.1	38.6	0.337

31

Table 2. Exploratory Factor Analysis of Baseline Neuropsychological Tests, N=681.

Test	Factor 1	Factor 2	Factor 3
Trails A	-.823		
Trails B	-.823		
UFOV Composite	-.761		
SDMT	.587		
DVT Errors		.876	
DVT Time		-.621	
COWAT Composite			.775
Stroop Word			.765
Stroop Color			.717
Stroop Color-Word			.699

Table 3.Pooled and Age-Stratum Specific Multiple Logistic Regression Results for$\geq$ 100 ms Improvements on the UFOV test at 6-8 Weeks Post-Randomization.

	Adjusted Odds Ratio	*P* value	Lower CI$_{95\%}$	Higher CI$_{95\%}$
Pooled Analysis with Both Age Strata (N = 616)				
Group 1	4.01	0.001	1.92	8.37
Group 2	5.52	0.001	2.63	11.59
Group 3	1.00	---	---	---
Group 4	5.15	0.001	2.55	10.42
UFOV at Randomization	1.01	0.001	1.01	1.02
Separate Analysis in the $\geq$ 65 Age Stratum (N = 207)				
Group 1	3.68	0.018	1.25	10.78
Group 2	5.52	0.002	1.85	16.47
Group 3	1.00	---	---	---
Group 4	5.14	0.002	1.80	14.71
UFOV at Randomization	1.01	0.001	1.01	1.01
Separate Analysis in the 50-64 Age Stratum (N = 409)				
Group 1	5.30	0.002	1.86	15.08
Group 2	6.91	0.001	2.41	19.84
Group 3	1.00	---	---	---
Group 4	6.00	0.001	2.23	16.15
UFOV at Randomization	1.02	0.002	1.01	1.02

Key: Group 1 = on-site *Road Tour* without boosters; Group 2 = on-site *Road Tour* with boosters; Group 3 = on-site attention control; and, Group 4 = at-home *Road Tour*.

34

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6-8
	2b	Specific objectives or hypotheses	8
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7-8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	na
Participants	4a	Eligibility criteria for participants	9-10
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8, 11-12
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	na
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	na
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	10

For peer review only

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	8, 10-11
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12-13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12-13
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	26
	13b	For each group, losses and exclusions after randomisation, together with reasons	26
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	na
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	28
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	26
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	15-16, 30
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	15-16, 30
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	14-15
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	na
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	4-5
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	4-5
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16-17
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	na
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ open

Post-training results from a randomized controlled trial to improve cognitive functioning in older adults: the Iowa Healthy and Active Minds Study

SCHOLARONE™
Manuscripts

Post-training results from a randomized controlled trial to improve cognitive

functioning in older adults:the Iowa Healthy and Active Minds Study

Fredric D. Wolinsky
Mark W. Vander Weg
M. Bryant Howren
Michael P. Jones
Rene Martin
Tana M. Luger
Kevin Duff
Christopher Goerdt
Steven Wolfe
Megan M. Dotson

Running Head: Post-training results from the IHAMS trial

Abstract

<u>Objectives</u>:The Iowa Healthy and Active Minds Study (IHAMS) is a four-arm, randomized controlled trial of a visual processing speed training program (*Road Tour*). This article presents the post-training results for the primary outcome.

<u>Design</u>:Within two age strata (50-64 vs. $\geq$ 65), 681 men and women attending general internal and family medicine clinics were randomized to four training groups: (1) a supervised, on-site, standard(10-hour) dose of*Road Tour* training;(2) a supervised, on-site,standard dose of *Road Tour* training with 4 hours of subsequent booster trainingscheduled to occur at 11-months post-randomization; (3) a supervised, on-site, standard dose of attention control training; and, (4) a self-administered, at-home, standard dose of*Road Tour* training. The primary outcome was the Useful Field of View (UFOV). Three intent-to-treat analyses were conducted, includingthe primary analysis with(a) multiple linear regression models of composite UFOV scores using Blomrank transformations, and secondary analyses with (b) general linear mixed effects models, and(c) multiple logistic regression models among the 620 participants (91%) with complete data.

<u>Results</u>: In the multiple linear regression analyses of the Blom rank transformed UFOV composite at post-training for both age strata, random assignment to any *Road Tour* training group vs. the attention control group was significant ($p<$ .001), with an effect size of -0.558 (adjusted for the Blom rank transformed UFOV test at randomization).Similarresults were obtained for each *Road Tour* group and within each age-stratum, as well as in the general linear and multiple logistic regression models.

Conclusion: A 10-hour dose of *Road Tour* training resulted in medium-sized post-training improvements in visual processing speed. *Road Tour* was equally effective whether administered under laboratory supervision or self-administered in the patient's home, and for participants in both age strata (50-64 vs. $\geq$ 65).

Clinical Trial Registration Number: NCT01165463.

3

Article Summary

Article Focus:

- Normative age-related declines in cognitive functioning leavea pressing need to identify efficient and effective training interventions for older adults.

- IHAMSis a four-arm RCT of three modes of delivering a computerized visual speed of processing intervention vs. an attention control group.

Key Messages:

- IHAMS is the first RCT to evaluate the efficacy and effectiveness of *Road Tour*, a second-generation computerized visual speed of processing intervention.

- Statistically significant medium-sized post-training improvements in visual processing speed were observed regardless of delivery method or age strata.

Strengths and Limitations of This Study:

- Strengths: this RCT uses a large sample of men and women $\geq$50 years old and overcomes four of the fiveimportant limitations (exclusion of 50-64 year olds, use of a no-contact control group, adherence-conditioned assignment to booster training, and reliance on a supervised cognitive training program) of a previous multi-site trial.

- Limitations: the sample was drawn from just one familycare center in which minorities were underrepresented, participants had to have a home computer and internet access, and data on the primary outcome were available only at randomization andpost-training.

Introduction

It is well established that age-related cognitive decline is a common, normal part of the aging process that occurs across many cognitive functions including memory, orientation, attention, abstract thinking, and perception [1-4]. These age-related cognitive changes can be viewed as the result of physical, behavioral, and environmental changes that combine to promote negative brain plasticity and degradations in functioning [5]. Fortunately, this capacity for physical and functional brain change across the lifespan is bi-directional [5,6].Indeed, just as brain plasticity can lead towards degradation in cognitive functioning with age, this same plasticity process can also be used to strengthen cognitive abilities [7-9]. This is especially important given recent evidence demonstrating that these age-related declines commence as early as age 28 and then continue in a linear fashion throughout the remainder of the life course [9].

Many training programs have been developed to help mitigate these age-related cognitive functioning declines. Although the gains associated with most earlier cognitive training interventions appeared to be highly task- and context-specific, more recent developments have demonstrated that improving the coordination of executive skills can transfer beyond the testing environment [7]. These often involvecomplex video games, task-switching paradigms, or divided attention tasks because these training platforms provide a carefully controlled and well-structured environment. Someof these successful interventionshave focused on improving visual information processing

5

speed, which is not surprising given the considerable evidence that supports the role of

processing speed in age-related cognitive decline [10-12].

Perhaps the most extensively evaluatedinterventionthat targets improving visual

processing speed is that developed by Ball and Roenker[4,13,14]. Their program trains

users to improve the speed and accuracy with which they identify and locate visual

information using a divided attention format. Over time, the difficulty and complexity of

each task is systematically increased as users attain specified performance criteria.

Manipulations to increase difficulty include decreasing visual stimuli duration, adding

visual or auditory distracters, increasing similarity between target and distracter stimuli,

and presenting visual targets over a broader spatial expanse. The basic tasks,

however, are always the same—central discrimination and peripheral target location.

Substantial evidence from the USA NIH-funded multi-site randomized controlled trial

(RCT) known as ACTIVE (Advanced Cognitive Training for Vital Elderly) has shown the

efficacy of Ball and Roenker's visual processing speed intervention on both immediate

and distal cognitive functioning, as well ason subsequent health outcomes [15-24].

Posit Science Corporation (San Francisco, California, USA) acquired the rights to

Ball and Roenker's visual speed of processing training program in 2007 [4,13,14].

While all of the original tasks were maintained, the delivery platform was modified to be

user-friendly and self-administered. Gaming elements were also added to improve user

engagement and enhance compliance. The resulting second-generation computerized

visual speed of processing training program is known as *Road Tour*, and has been

commercially available since 2009 as part of the*Insight*^tm visual processing speed suite

(which includes four other visual training programs known as *Bird Safari, Jewel Diver,*

6

Master Gardener, and Sweep Seeker), or as part of the *DriveSharp^tm* driving suite (which also includes *Jewel Diver* and *Sweep Seeker*) (http://www.positscience.com/our-products).

We designed the Iowa Healthy and Active Minds Study (IHAMS) to evaluate the efficacy and effectiveness of *Road Tour*. IHAMS is a four-group parallel RCT (NCT01165463) whose protocol has been described in detail elsewhere [25]. In this article we report on the post-training (6-8 weeks post-randomization) results for the primary outcome. Because no standard booster training occurred by this time, and because supplemental training beyond 10 hours in the at-home group should have been minimal, we hypothesize that participants randomized to any of the three *Road Tour* training groups (no booster training subsequently scheduled, booster training scheduled to occur at 11 months post-randomization, and at-home training with self-dosing allowed after 6-8 weeks post-randomization) should have significantly and similarly greater improvements in visual processing speed immediately after training than the attention control group.

Methods and Analysis

Overview. Figure 1 shows the IHAMS study design and participant recruitment results. IHAMS used a 3:3:4:4 allocation ratio and block randomization separately within two age-strata (50-64 [mean = 57.2, standard deviation = 4.2, range = 50-64] vs. $\geq$ 65 [mean = 71.4, standard deviation = 5.7, range = 65-87]). A total of 681 participants were randomized to one of the following groups: (1) 10 hours (a single two-hour session each week over the first 5-6 weeks) of supervised on-site training using *Road Tour* (N = 154), (2) 10 hours of supervised on-site training using *Road Tour* plus 4 hours of booster training at 11 months post-randomization (N = 148), (3) 10 hours of

7

supervised on-site attention control using computerized crossword puzzles (*Boatload of Crosswords*, Boatload Puzzles, LLC, Yorktown Heights, New York, USA) (N = 188), or (4) self-administered at-home training using *Road Tour* for 10 hours or more (N = 191), with the option to continue using *Road Tour* thereafter but not to use any of the four other training programs from the *Insight* software suite until the study was over. Post-training assessments occurred at 6-8 weeks post-randomization, and complete baseline and post-training data were obtained for 620 participants (91%). One-year post-randomization assessments are scheduled to be completed by late November 2011. IHAMS was sized to provide $\geq$ 80% power to detect an effect size of 0.25 in the primary outcome at one-year post-randomization with alpha = 0.05.

Sampling Frame. We includedall patients attending either the general internal or family medicine clinics of the University of Iowa'sFamily Care Center (FCC) in the IHAMS sampling frame. The electronic medical recordwas used for initially selecting potentially eligible participants. The initial inclusion criteria were: (1) age $\geq$ 50 years old, (2) $\geq$ 2 visits to a primary care physician in the FCCin the past year, and (3) the absence ofdiagnostic codes for Alzheimer's or Picks' disease, arteriosclerotic dementia, other senile or pre-senile dementia, dementia due to alcohol or drugs, amnestic syndrome, or dementia due to other organic conditions. A total of 5,743 potentially eligible patients were identified. Weekly random replicates of 100-250 of them were sent a letter describing the study and asking them to telephone the project office and indicate whether or not they were interested in participating.

Telephone Screening. We attempted to further screen all potentially eligible patients, but could not reach 1,627. Of the 4,116 remaining potentially eligible patients,

2,079 declined to participate, and 966 had not yet been mailed their letter describing the study by the time that study enrollment was closed, leaving 1,071 potentially eligible patients. We conducted brief screening interviews to identify who among them met any of the following exclusion criteria: (1) significant cognitive impairment based on ≥ 3 errors on a 10-item mental status exam (N = 15)[26], (2) significant self-reported uncorrected visual acuity problems (N = 63), (3) not having a personal computerwith a CD-ROM in the home (N = 303), (4) not having internet access (N = 8), or (5) having previously used a computerized program for improving cognitive function (N = 1). This resulted in the exclusion of 390 potential participants.

Informed Consent and Baseline Interviews. After completing the screening interview, eligible patients were scheduled for a two-hour visitto our laboratory where written informed consent was obtained for the 681 participants who were enrolled between March 22 and November 16, 2010. The 681 enrolleeswere then administered their baseline (randomization) interviews by trained research assistants using computer-assisted interviewing protocols. Immediately afterwards each participant was randomized to one of the four study groups.

Randomization Procedure. The study biostatistician (MPJ) determined the order of assignments using a computer-generated list of random numbers and a 3:3:4:4 allocation ratio, because the first two groups can be pooled for some analyses. Sample size was based on *a priori* power calculations to achieve 80% power at alpha = 0.05 for a two-tailed test with a 0.25 effect size between each training group and the attention control group at one-year post-randomization. Block randomization was used to maintain balance on the two age-strata (50-64 and $\geq$ 65). Block sizes of 4, 8, and 12

9

were randomly varied. The assignment for each participant's ID number was recorded on a participant letter and then sealed in an opaque envelope with only the ID number visible. Two age-stratum specific boxes containing the assignment envelopes were stored in a locked cabinet in the Project Coordinator's office. The Project Coordinator (MMD) had the responsibility of unsealing the envelope (from the appropriate age-stratum box) and revealing each participant's group assignment.

Cognitive Processing Speed Outcomes. The six neuropsychological assessments, which were all administered at randomization and are being administered at one-year post-randomization, are: (1) the UFOV PC mouse version [27]; (2) the Symbol Digit Modalities Test (SDMT) [28]; (3) the Trail Making A and B Tests (TMT) [29]; (4) the Controlled Oral Word Association Test (COWAT) [30]; (5) the Digit Vigilance Test (DVT) [31]; and, (6) the Stroop Color and Word Test (Stroop) [32]. The UFOV test is the primary outcome and earlier versions of it have been used in most prior visual speed of processing studies, including ACTIVE. It was also administered at post-training (6-8 weeks post-baseline). The UFOV includes three subtests—stimulus identification, divided attention, and selective attention—each of which is scored from 17-500 milliseconds (ms) reflecting the shortest exposure time at which the participant could correctly perform each subtest 75% of the time, with a composite ms outcome score ranging from 51-1500 ms. Consistent with the main reports from the ACTIVE trial [16, 17], we used Blom rank transformations [33] on the UFOV composite scores at randomization and post-training to normalize the distributions for the multiple linear regression and general linear mixed effects models. The Blom rank transformations resulted in means of zero and standard deviations of unity, and more nearly Gaussian

distributions. Blom transformations are commonly used for distributional normalization [34], and have been shown to yield the most reliable results among a variety of alternatives for violations of the distributional assumptions of both multiple linear regression and general linear mixed effects models[35].

The SDMT, TMT, COWAT, DVT, and Stroop tests are secondary outcome measures, but were not administered at post-training due to time constraints. SDMT captures divided attention and processing speed, and is based on how many of 110 possible digit-symbol pairs were scored as correct pairs by the participant in 90 seconds. TMT assesses visual scanning ability, processing speed, and set-shifting/executive functioning, and is coded as the number of seconds needed to correctly complete connecting the number and number-letter sets. COWAT assesses verbal fluency based on the number of unique words beginning with the letter C (or F or L in the second and third trials) generated by the participant during 60 seconds, with a composite score of the number of correct words used across the three letter trials. DVT assesses sustained attention and psychomotor speed, is performed by crossing out randomly placed 6's in 59 rows of numbers, and is scored as the error and time totals. The Stroop assesses processing speed and executive functioning, and is scored as the correct number of words, colors, and color-words identified in 45 seconds on each subtest.

The *Road Tour* Training Program. *Road Tour's* basic appearance to the user is shown in Figure 2a. After clicking on the start button to initiate training, Figure 2b is shown. Here, both the license plate area and the eight circular locations in the near orbit surrounding it are empty. The empty license plate is then replaced, as in Figure

11

2c, with the target vehicle, either a car or a truck. Similarly, the eight empty circular

locations surrounding the license plate are then replaced with seven distracter stimuli

(rabbit crossing signs) or the target sign (Route 66). The stimuli (car vs. truck, and

rabbit crossing vs. Route 66 sign) are presented for a specified time and are then

replaced by Figure 2d. The amount of time that Figure 2c remains on the screen before

being replaced by Figure 2d is measured in ms. In Figure 2e, both target vehicles (the

car and truck) are presented in the center of the screen, one of which was previously

shown in Figure 2c as the target vehicle. The user first clicks on the correct target

vehicle (car or truck), and then on the circular location where the correct peripheral

target (Route 66 sign) appeared (Figure 2f). The goal is to improve cognitive

processing speed by progressively reducing the ms of exposure that Figure 2c remains

on the screen with subsequent correct identification of both the stimuli (target car or

truck) and target (Route 66) sign. As the user progresses, three changes occur which

further increase task difficulty: (a) the target visual field expands by progressing

outward from the license plate to add medium and distal orbits, (b) these are

accompanied by an increasing number of distracters to fully populate all three orbits (up

to 47), and (c) the vehicle pairs morph through 9 different stages or pairs to become

more similar and thus more difficult to differentiate.

Analysis. First, one-way analysis of variance for selected participant

characteristics, training time, and the six neuropsychological outcomes was conducted.

To assess the effects of *Road Tour* training (vs. attention control training) on the primary

outcome, we used three intent-to-treat analytic approaches, including (a) multiple linear

regression of composite UFOV scores using Blom rank transformations for

normalization (the primary analysis specified in the protocol [25]), (b) general linear

mixed effects models using the Blom rank transformations (as a secondary analysis),

and (c) multiple logistic regression analyses of post-training improvements ≥ 100

milliseconds in the non-transformed UFOV composite (also as a secondary analysis).

In each approach, our first model involved the single binary contrast of being randomly

assigned to any *Road Tour* training, adjusting for the valueof the UFOV composite at

randomization. We then substituted three mutually exclusive binary indicators for the

single binary contrast. These three binary indicators reflect whether the participantwas

in the on-site speed of processing intervention without boosters, the on-site speed of

processing intervention with boosters subsequently scheduled to occur at 11 months

post-randomization, or the at-home speed of processing group vs. those in the on-site

crossword puzzle (attention control) group as the reference or omitted category. We

then estimated both the first and second model separately within each age stratum.

Results

Baseline Group Comparisons. Table 1 compares the four training groups on

selected participant characteristics (including the self-rated health and change in self-

rated health from one-year ago items from the SF-36 [36]), amount of training (in

minutes) received, and the fivesecondary outcome neuropsychological tests at

randomization. No statistically significant differences were found for any of the

participant characteristics. Statistically significant differences were observed, however,

on the amount of training received. The attention control group received the most

training, while the at-home *Road Tour* training group received the least (despite

instructions to the contrary, 37 of them used one or more of the four other programs in

the *Insight* suite during training, but only 12 did so for more than 14 minutes). This is not surprising given the efforts to schedule the five, two-hour training sessions for all participants in the three on-site training groups. Moreover, on-site *Road Tour* participants were allowed to stop their training once they had completed all 81 of the available exercise sets, which occurred about 5% of the time. Finally, although *Road Tour* directly monitors training in minutes based on actual program usage, participant training in the attention control group was monitored by project staff based on the completion of two-hour training sessions.

Statistically significant differences between the training groups were also observed for the SDMT, TMT (A and B), and the word and color sub-tests of the Stroop. In all cases, the attention control group demonstrated the lowest level of performance. These differences, however, were modest in the absolute, although *post-hoc* comparisons using Dunnett tests found 8 of the 15 group level contrasts involving the attention control group to be statistically significant. The attention control group had significantly lower performance than (a) all three training groups on the TMT-A, (b) the on-site training group without subsequent scheduled boosters on the SDMT, TMT-B, and the Stroop color subtest, and (c) the on-site training group without subsequent scheduled boosters and the at-home training group on the Stroop word subtest. Therefore, we will adjust for these differences in all subsequent analyses by including the value of the outcome measure at randomization.

Table 2 compares the four training groups on the three UFOV subtests—stimulus identification, divided attention, and selective attention—as well as the UFOV composite and Blom rank transformed UFOV composites at randomization and at post-training.

14

No statistically significant differences were observed on the three UFOV subtests, the UFOV composite,or the Blom rank transformed UFOV composite scores at randomization, although the attention control group had the slowest performancein all comparisons. At post-training, however, statistically significant differences were observed on the three UFOV subtests, on the UFOV composite score, and on the Blom rank transformed UFOV composite score. Moreover, Dunnett tests indicated that all of the training group comparisons involving the attention control group were statistically significant as well.

Multiple Linear Regression. The first panel of Table 3 contains the results from the multiple linear regression analysis of the Blom rank transformed UFOV composite scores at post-training predicted by the Blom rank transformed UFOV composite scores at randomization and the single binary contrast of being randomly assigned to any *Road Tour* training for all 620 IHAMS participants with complete data. The second and third panels contain the results from similar analyses stratified on age (50-64 vs. $\geq$ 65). Because the Blom rank transformed UFOV composite scores have been normalized to have a mean of zero and a standard deviation of unity, the unstandardized *b* coefficients shown may be directly interpreted as effect size estimates. The effect sizes are -0.558 in the pooled analysis, -0.479 for the $\geq$ 65 age stratum, and -0.626 for the 50-64 age stratum, with all three *p* values < 0.001. Although the magnitude of the effect sizes appear larger in the younger age stratum than in the older age stratum, note that all effect sizes are within the 95% confidence intervals of each other, and are thus functionally comparable. This was verified by adding a binary marker for age strata and

15

its interaction with having any *Road Tour* training to the model, neither of which were statistically significant.

Table 4 contains the results from the multiple linear regression analysis of the Blom rank transformed UFOV composite scores when the single binary contrast of being randomly assigned to any *Road Tour* training is replaced by the set of three binary indicators reflecting each specific *Road Tour* training group. As in Table 3, the first panel of Table 4 contains the results for all 620 IHAMS participants with complete data, while the second and third panels contain the results from analyses stratified on age (50-64 vs. $\geq$ 65). Also as in Table 3, all of the coefficients shown may be directly interpreted as effect size estimates, and all have *p* values < 0.001. The effect sizes in Table 4 for each of the *Road Tour* training groups are very similar to those shown in Table 3 for the pooled markers. Here, too, the magnitude of the effect sizes for each training group appears larger in the younger age stratum than in the older age stratum, but once again all effect sizes are within the 95% confidence intervals of each other, and are thus functionally comparable. Similarly, while the effect sizes within panels appears smallest for the on-site training group not scheduled to receive subsequent booster training, only for the younger age stratum do these lie outside of each other's 95% confidence intervals, and then only when compared to the at-home training group.Taken together, the multiple linear regression results contained in Tables 3 and 4 support our hypothesis for the post-trainingeffects in all respects.

General Linear Models with Mixed Effects. We used general linear models with mixed effects as a secondary analytic approach to adjust for the correlated errors within participants that may arise from the repeated UFOV measurement (which the primary

16

multiple linear regression analyses do not address [37]). The results from the general linear mixed effects model for the effect of being randomly assigned to any *Road Tour* training for all 620 IHAMS participants with complete data revealed (data not shown) a statistically significant (*p* < 0.001) interaction between the Blom rank transformed outcome and any *Road Tour* training reflecting a standardized mean difference (effect size) of -0.430. When this model was run separately within age strata, the standardized mean difference was -0.378 (*p*< 0.001) in the older stratum and -0.490 (*p*< 0.001) in the younger stratum. Once again, although these effects sizes appear larger in the younger stratum, these differences were not statistically significant, as indicated when the binary marker for age strata and its interaction with any *Road Tour* training (a group-by-time-by-age-stratum interaction) was added to the general linear model for all IHAMS participants.

When the single binary contrast of being randomly assigned to any *Road Tour* training was replaced by the set of three binary indicators reflecting each specific *Road Tour* training group for all IHAMS participants, standardized mean differences (compared to the attention control group) of -0.356, -0.448, and -0.475 were obtained for the *Road Tour* without subsequently scheduled booster training, *Road Tour* with subsequently scheduled booster training, and at-home *Road Tour* training groups, all of which were statistically significant (p < 0.001). Similar results were obtained when this general linear model was estimated within age strata. Once again, no group-by-time-by-age-stratum interactions were observed in the general linear mixed effects model for all IHAMS participants. Thus, when taken together, the general linear mixed effects modeling results also support our hypothesis for the post-trainingeffects in all respects.

Multiple Logistic Regression. The multiple logistic regression analysis was conducted to ensure that both analyses of the Blom rank transformed UFOV composites were not statistical artifacts of the normalization algorithm. An effect threshold of improvements $\geq$ 100 ms was chosen because it represents an effect size of 0.55 based on the non-transformed baseline UFOV composite, which is equivalent to that observed in Table 3 for the pooled analysis of assignment to any *Road Tour* training in the overall IHAMS sample. The adjusted odds ratio (*AOR*) for being randomized to any *Road Tour* training group on achieving a post-training improvement in the UFOV test $\geq$ 100 ms was 4.85 (*p*< .001). The absolute improvement effect was 12.2% (34.3% of *Road Tour* subjects improved $\geq$ 100 ms vs. 23.1% or attention control subjects). This simple model fit the data extremely well (*Area under the Curve* [*AUC*] = 0.92). We then replaced the single binary marker with the three indicators for each of the *Road Tour* training groups, and found that while the three *Road Tour* training groups' *AORs* varied from 4.01 to 5.52 (*p* values< .001; *AUC* = 0.92; absolute improvement effects 10.0% to 12.5%), they all fell within the others' confidence intervals, reflecting similar effect sizes. Comparable results were found (not shown) within age strata, although the model for the younger age stratum fit the data slightly better (*AUC* = 0.95 vs. *AUC* = 0.86). Thus, when taken together, these multiple logistic regression results also confirm support our hypothesis for the post-training effects in all respects.

Conclusion

Gradual cognitive decline is nearly universal and is well-recognized as a normal part of the aging process. According to Salthouse [38], most age-related cognitive deteriorations are at least partially attributable to declines in information processing speed, which affects episodic and working memory, verbal fluency, and reasoning

18

abilities. Previous work, especially the USA NIH-funded multi-site ACTIVE trial has led to the development of a promising, second-generation computer-based intervention to improve visual processing speed known as *Road Tour*. We designed IHAMS to assess the efficacy and effectiveness of *Road Tour*.

There are five important aspects of IHAMS that warrant further mention. First, IHAMS overcomes five major limitations of the previous USA NIH-funded ACTIVE multi-site RCT, the first three of which we were able to directly evaluate in this article reporting on the post-training results. In addition to participants 65 years old or older, IHAMS included 50-64 year olds to determine whether speed of processing training is efficacious and effective before substantial cognitive decline occurs in the seventh decade [39]. If speed of processing training is efficacious in this younger cohort, preventative interventions could focus on improving cognitive functioning before the rapid age-related declination process even begins. IHAMS also used an attention control group that was trained on computerized crossword puzzles rather than a no-contact control group. This allowed us to directly evaluate the potential that placebo effects cloud the interpretation of the results from ACTIVE [25]. By using *Road Tour* rather than its predecessor, IHAMS avoids reliance on a supervised training intervention. This allowed us to directly evaluate whether sending participants home with the software to use on their own PCs is efficacious, and if so, whether it was as effective as supervised on-site training, which potentially expands substantially the ability to implement widespread public health interventions. IHAMS also directly randomizedparticipants to receive or not receive on-site booster training, as opposed to the adherence-conditioned assignment to booster training used in ACTIVE. When the

one-year follow-up data become available, this will allow us to separate the effects associated with standard dosing from those derived from standard dosing plus booster training. IHAMS also included five additional neuropsychological tests assessed at baseline that will also be assessed at the one-year follow-up as secondary outcomes. Once the one-year follow-up data become available, this will allow us to assess the extent to which *Road Tour* effects on the primary outcome transfer to the other cognitive functions tapped by these neuropsychological tests.

The second important aspect of this study involves the training intervention itself. *Road Tour* is easy to use on any PC (versions for both PC and Apple platforms are available) at any location. Adherence to training was remarkable, even in the at-home training group which did not benefit from the support of weekly scheduling contacts. The targeted standard training dose was just 10 hours, although the mean amount of time that it was used in the two on-site training groups was only 7.8 hours spread over a five-week period. The two-hour training sessions were extremely well-tolerated, and no discomfort of any kind was reported by any participant during delivery of the standard training dose. In sum, the ability to readily implement *Road Tour* training in widespread public health interventions is extremely promising from a logistics perspective.

The demonstrated efficacy of *Road Tour* to improve UFOV scores is the third important aspect of this study that warrants further mention. Three different analytic approaches—multiple linear regression, general linear mixed effects, and multiple logistic regression models—all substantially supported our hypothesis for the post-training effects in all respects. The primary analytic approach was the pooled multiple linear regression of the Blom rank transformed UFOV composite at post-training. When

these analyses were done pooling both age strata, the regression coefficient for random assignment to any *Road Tour* training group vs. the attention control group was statistically significant (p< .001) with an effect size of -0.558 (adjusted for the Blom rank transformed UFOV test at randomization). Similar results were also obtained when comparing each of the three training groups with the attention control group. That this medium effect size was obtained with an average of less than eight hours of training suggests that the potential for widespread public health interventions is very promising.

Directly comparing the efficacy of *Road Tour* obtained in IHAMS to the speed of processing training results obtained from a meta-analysis consisting of ACTIVE and five other visual speed of processing training RCTs with a total enrollment of 907 subjects followed for varying time lengths [13] is problematic for at least four reasons. First,most of those RCTsused the touchscreen version of the UFOV which has four subtests and yields a composite score that ranges between 68 and 2,000 ms, while IHAMS used the PC mouse version which has only three subtests and yields a composite score that ranges between 51 and 1,500 ms.Second, most of those RCTs used a no-contact control groupdesign which added any potential placebo effect to their training effect estimates. Moreover, IHAMS used an attention control group that was trained using a computerized crossword puzzle program that may have led to some improvement in processing speed beyond the potential placebo effect. Third, all of those RCTs used the predecessor version of the speed of processing software that required supervised, on-site training. Fourth, IHAMS used less robust mental status and self-reported visual acuity screening tools than those RCTs for exclusion purposes, which enhancesthe generalizability of IHAMS while biasingits effect size estimates toward the null. That

21

said, the meta-analysis [13] revealed an average effect size estimate of -0.81, which is somewhat larger than the two-year -0.72 effect size estimated just from ACTIVE. Taking the three differences noted above into consideration, the effect sizes for those six RCTs are quite comparable to the post-training effect size estimated from our multiple linear regression model of -0.56 and from our general linear mixed effects model of -0.43.

The fourth important aspect of this study that warrants further mention involves the comparison of the on-site vs. the at-home training effects. For the two on-site *Road Tour* training groups, the effect size estimates from the multiple linear regression modelwere-0.457 and -0.585, while the effect size estimate for the at-home training groupwas -0.629. Thus, the effect size was largest for the at-home training group, although all three estimates are within the others' 95% confidence intervals, reflecting their comparability. Therefore, the benefits that accrue from *Road Tour* training can be achieved using a home PC without supervision, which substantially increases the opportunity to implement speed of processing training in widespread public health interventions.

The final aspect of this study that warrants further mention involves the efficacy equivalence between the two age strata. Among older adults ($\geq$ 65 years old) the estimated effect size from the multiple linear regression analysis was -0.479, while it was -0.626 among younger adults (50-64 years old). Moreover, when an interaction term was added to the model in the pooled analysis, no statistical difference in these estimates was observed. This finding of equivalence in the efficacy of *Road Tour*between the age strata is extremely promising because it suggests that

22

preventative interventions could focus on improving cognitive functioning at an earlier stage of age-related declinege.

In conclusion, we note that although our study has numerous strengths, it does have limitations, four of which are worth noting. First,although large, the sample was drawn from just one family care center in which minorities were underrepresented. Second, to be eligible, participants had to have a home computer and internet access. Third, only one of the five training programs included in Posit Science's *Insight* suite (*Road Tour*) was studied. Finally, only data on the primary outcome were available, and then only at randomization and post-training. The first two of these limitations constrain the generalizability of IHAMS somewhat, while the last two leave the issues of potential benefits from multifaceted training (using all five of the training programs in the *Insight* suite) and the transferability to the five other neuropsychological outcomes unresolved.

End Matter

Competing Interests:The *Road Tour* computerized visual speed of processingintervention used in IHAMS is commercially available from Posit Science Corporation (San Francisco, CA, USA).None of the members of the investigative team have any conflicts of interest or commitment involving Posit Science. Specifically, no one on the investigative team will financially profit in any way from the use of *Road Tour*.

Posit Science acquired ownership in October 2007 of Ball and Roenker's [4,13,14] original speed of processing intervention that was used in the multi-site ACTIVE RCT on which FDW was an original co-investigator (at the ACTIVE Indiana University site). In collaboration with Professors Ball and Roenker, Posit Science subsequently developed the second-generation, value-added version of the visual speed of processing intervention known as *Road Tour* and used here in IHAMS. From December 2007 to March 2009, FDW had a limited, part-time consulting arrangement (15 days, total) with Posit Science to support additional analyses of the first five-years of the ACTIVE follow-up data that had not been identified in the original ACTIVE protocols nor funded by the various US NIH grants supporting ACTIVE. This arrangement was

24

approved in advance by the ACTIVE Executive Committee (which included the US NIH project officers), and was sanctioned by the Provost of the University of Iowa.

After terminating this limited, part-time consulting arrangement with Posit Science, FDW applied in April 2009 for, and was awarded in September 2009 the US NIH Challenge Grant known as IHAMS. Posit Science provided the 700 copies of *Road Tour* used in IHAMS at no cost or obligation. Furthermore, in its letter of commitment to IHAMS and the US NIH, Posit Science stated should the results support the efficacy and effectiveness of *Road* Tour, they will "work with agencies at the federal government to make the program available for wide-scale implementation at only a fraction of the current per-user cost."

Ethics Approval: Ethics approval was provided by the University of Iowa Institutional Review Board (IRB-03; IRB protocol number 200908789), initially approved on September 12, 2009, and most recently re-approved on May 18, 2011.

Contributors:FDW is the principal investigator on the study, wrote the original proposal, supervised the trial, conducted all of the analyses, and drafted the manuscript. MWV-W is co-principal investigator on the study, collaborated on the original proposal, co-supervised the trial, and reviewed the analyses reported here as well as the manuscript itself. MBH is a post-doctoral fellow working on the study, trained all of the interviewers, supervised the scoring of the neuropsychological tests, and reviewed the manuscript. MPJ is the study biostatistician, devised the randomization protocol, reviewed all of the analyses, and reviewed the manuscript. RM is a co-investigator on the study, collaborated on the original proposal, supervised preparation of all of the ethics, consent, and IRB documents, and reviewed the analyses and the manuscript.

TML was a study Research Assistant who assisted with piloting the interview protocol,

conducted randomization interviews, and reviewed the manuscript. KD is the study

neuropsychologist, supervised selection of the neuropsychological tests, reviewed the

psychometric analyses, and reviewed the manuscript. CG is the medical director of the

FCCGeneral Medicine Clinic, participated in subject recruitment, and reviewed the

manuscript. SW is the medical director of the FCC Family Medicine Clinic, participated

in subject recruitment, and reviewed the manuscript. MMD is the Project Coordinator.

References

1. Birren JE, Woods AM, & Williams MV. Behavioral slowing with age: causes, organization, and consequences of slowing. Pp. 293–308 in Poon LW (ed), *Aging in the 1980s: psychological issues*. Washington, DC: American Psychological Association, 1980.

2. Edwards JD, Wadley VG, Myers RS, Roenker DL, Cissell GM, & Ball KK. Transfer of a speed of processing intervention to near and far cognitive functions. *Gerontol*, 2002;48:329–340.

3. Madden DJ. Four to ten milliseconds per year: age-related slowing of visual word identification. *J Gerontol: Psych Sci*, 1992;47:P59–P68.

4. Roenker DL, Cissell GM, Ball KK, Wadley VG, & Edwards JD. Speed-of-processing and driving simulator training result in improved driving performance. *Hum Factors*, 2003;45:218–233.

5. Mahncke HW, Bronstone A, & Merzenich MM. Brain plasticity and functional losses in the aged: scientific bases for a novel intervention. *Prog Brain Res*, 2006;157:81-109.

6. Greenwood PM. Functional plasticity in cognitive aging: review and hypothesis. *Neuropsychol*, 2007;21:657-673.

7. Hertzog C, Kramer AF, Wilson RS, &Lindenberger U. Enrichment effects on adult cognitive development: can the functional capacity of older adults be preserved and enhanced? *PsycholSci Pub Interest*, 2008;9:1-65.

8. Salthouse TA. Consequences of age-related cognitive declines. *Ann Rev Psychol*, 2012;63: in press.

27

9. Salthouse TA. When does age-related cognitive decline begin? *Neurobiol Aging*,
    2009;30:507-514.

10. Clay OJ, Edwards JD, Ross LA, Okonkwo O, Wadley VG, Roth DL, & Ball KK.
    Visual function and cognitive speed of processing mediate age-related decline in
    memory span and fluid intelligence. *J Aging Health*, 2009;21:547-566.

11. Lemke U, &Zimprich D. Longitudinal changes in memory performance and
    processing speed in old age. *Aging, Neuropsychol, Cog*, 2005;12:57–77.

12. Zimprich DM. Can longitudinal changes in processing speed explain longitudinal
    changes in fluid intelligence? *Psychol Aging*, 2002;17:690–695.

13. Ball KK, Edwards JD, & Ross LA. The impact of speed of processing training on
    cognitive and everyday functions. *J Gerontol: SocSci*, 2007;62B:19-31.

14. Ball KK, Beard BL, Roenker DL, Miller RL, & Griggs DS. Age and visual search:
    expanding the useful field of view. *J Optic SocAmer*, 1988;5:2210-2219.

15. Jobe JB, Smith DM, Ball KK, Tennstedt SL, Marsiske M, Willis SL, Rebok GW,
    Morris JN, Helmers KF, Leveck MD, &Kleinman K. ACTIVE: a cognitive
    intervention trial to promote independence in older adults. *Controlled Clin Trials*,
    2001;22:453-479.

16. Ball KK, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, Morris JN,
    Rebok GW, Smith DM, Tennstedt SL, Unverzagt FW, & Willis SL. Effects of
    cognitive training interventions with older adults: a randomized controlled trial.
    JAMA, 2002;288:2271-2281.

17. Willis SL, Tennstedt SL, Marsiske M, Ball KK, Elias J, Mann-Koepke K, Morris JN,
    Rebok GW, Unverzagt FW, Stoddard A, & Wright E. Long-term effects of

cognitive training on everyday functional outcomes in older adults. *JAMA*, 2006;296:2805-2814.

18. Wolinsky FD, Mahncke HW, Kosinksi M, Unverzagt FW, Smith DM, Jones R, Stoddard A, &Tennstedt SL. The ACTIVE cognitive training trial and predicted medical expenditures. *BMC Health Serv Res*, 2009;9:109:1-9.

19. Wolinsky FD, Unverzagt FW, Smith DM, Jones R, Wright E, &Tennstedt S. The effects of the ACTIVE cognitive training interventions on clinically relevant declines in health-related quality of life. *J Gerontol: SocSci*, 2006;61B:S281-S287.

20. Wolinsky FD, Unverzagt FW, Smith DM, Jones R, Stoddard A, &Tennstedt S. The ACTIVE cognitive training trial and health-related quality of life: protection that lasts for five years. *J Gerontol: Med Sci*, 2006;61A:1324-1329.

21. Wolinsky FD, Vander Weg MW, Martin R, Unverzagt FW, Ball KK, Jones R, &Tennstedt SL. The effect of speed of processing training on depressive symptoms in ACTIVE. *J Gerontol: Med Sci*, 2009;64A:468-472.

22. Wolinsky FD, Mahncke HW, Vander Weg MW, Martin R, Unverzagt FW, Ball KK, Jones R, &Tennstedt SL. The ACTIVE cognitive training interventions and the onset of and recovery from suspected clinical depression. *J Gerontol: PsycholSci*, 2009;64B:577-585.

23. Wolinsky FD, Mahncke HW, Vander Weg MW, Martin R, Unverzagt FW, Ball KK, Jones R, &Tennstedt SL. Speed of processing training improves self-rated health in older adults: enduring effects observed in the multi-site ACTIVE study. *IntPsychogeriatr*, 2010;22:470-478.

29

24. Wolinsky FD, Vander Weg MW, Martin R, Unverzagt FW, Willis SL, Marsiske M, Rebok GW, Morris JN, Ball KK, &Tennstedt SL. Cognitive training improves internal locus of control among older adults. *J Gerontol: SocSci*, 2010;65B:470-478.

25. Wolinsky FD, Vander Weg MW, Howren MB, Jones MP, Martin R, Luger TM, Duff K, Goerdt C, Wolfe S, & Dotson M. Protocol for a randomized controlled trial to improve cognitive functioning in older adults: the Iowa Healthy and Active Minds Study. *BMJ Open*, 2011-000218, in press.

26. Pfeiffer EA. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc*. 1975;23:433-41.

27. Edwards JD, Vance DE, Wadley VG, Cissel GM, Roenker DL, & Ball KK. Reliability and validity of Useful Field of View test scores as administered by personal computer. *J ClinExperNeuropsychol*, 2005;27:529–543.

28. Smith A. *Symbol digit modality test*. Los Angeles, CA: Western Psychological Services, 1982.

29. Reitan RM,&Wolfson, D. *The Halstead-Reitanneuropsychological test battery: therapy and clinical interpretation*. Tucson, AZ: Neuropsychological Press, 1985.

30. Benton AL, Hamsher K, &Silvan AB. *Multilingual aphasia examination* (3rd Edition). Iowa City, IA: AJA Associates, 1994.

31. Lewis R,&Rennick PM. *Manual for the repeatable cognitive-perceptual-motor battery*. Gross Point, MI: Axon, 1979.

32. Golden CJ. *The Stroopcolor and word test*. Chicago, IL: Stoelting Company, 1978.

33. Blom G. *Statistical estimates and transformed beta-variables*. New York, NY: Wiley, 1958

34. Measley TM, Erickson S, Allison DB. Rank-based inverse normal transformations are increasingly used, but are they merited?*Behav Genetics* 2009;39:580-585.

35. Kraja AT, Corbett J, Ping A, Lin RS, Jacobsen PA, Crosswhite M, Borecki IB, Province MA. Rheumatoid arthritis, item response theory, Blom transformation, and mixed models.*BMC Proceedings* 2007;1:S116.

36. McHorney CA, Ware JE, &Raczek R. The MOS 36-Item Short-Form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*, 1993;31:247-263.

37. Fox J. *Applied regression analysis and generalized linear models, 2nd ed*. Newberry Park, CA: Sage, 2008.

38. Salthouse TA. The processing-speed theory of adult age differences in cognition. *Psychol Rev*, 1996;103:403-428.

39. Salthouse TA. The paradox of cognitive change. *J ClinExperNeuropsychol*, 2010;332:622-629.

Table 1.Means and Standard Deviations (in Parentheses)of Selected Participant Characteristics and the Five Secondary Outcome Neuropsychological Tests at Randomization by Training group Status, N = 681.

Variable	Overall N=681	Road Tour On-Site No Boosters N=154	Road Tour On-Site With Boosters N=148	Attention Control On-Site N=188	Road Tour At-Home N=191	p value
Personal Characteristics						
Age (years)	61.9 (8.2)	61.4 (8.1)	62.5 (8.2)	61.8 (8.7)	61.9 (7.9)	0.676
Men (%)	37.3 (0.5)	37.2 (0.5)	32.5 (0.5)	42.0 (0.5)	36.7 (0.5)	0.340
Married (%)	69.9 (0.5)	73.0 (0.5)	61.0 (0.5)	73.4 (0.4)	71.2 (0.5)	0.053
Single (%)	11.2 (0.3)	10.1 (0.3)	14.9 (0.4)	8.0 (0.3)	12.0 (0.3)	0.219
Working (%)	54.5 (0.5)	56.8 (0.5)	53.9 (0.5)	50.0 (0.5)	57.6 (0.6)	0.459
Retired (%)	35.5 (0.4)	35.1 (0.5)	36.4 (0.4)	34.2 (0.5)	34.6 (0.3)	0.982
Income $\leq$ \$35K (%)	28.3 (0.5)	24.3 (0.4)	36.4 (0.5)	27.7 (0.5)	25.7 (0.4)	0.079
Income $\geq$ \$75K (%)	46.6 (0.5)	45.3 (0.5)	41.6 (0.4)	47.3 (0.5)	50.8 (0.5)	0.383
Self-Rated Health (5=best 1=worst)	3.8 (0.9)	3.8 (0.9)	3.8 (0.8)	3.7 (0.9)	3.9 (0.8)	0.526
One-Year Change in Self-Rated Health(5=best 1 =worst)	3.2 (0.8)	3.3 (0.8)	3.3 (0.8)	3.2 (0.8)	3.3 (0.7)	0.646
Training Time						
Minutes of Training	469 (217)	450 (199)	488 (151)	535 (154)	404 (295)	0.001
Neuropsychological Tests						
SDMT (# correct)	50.5 (9.4)	51.8 (9.0)	50.5 (9.5)	48.7 (9.3)	51.1 (9.6)	0.015

Table 1.Continued.

Variable	Overall N=681	*Road Tour* On-Site No Boosters N=154	*Road Tour* On-Site With Boosters N=148	Attention Control On-Site N=188	*Road Tour* At-Home N=191	*p* value
Trails A (sec)	41.9 (13.3)	40.9 (10.9)	39.8 (12.3)	45.0 (16.3)	41.2 (12.0)	0.001
Trails B (sec)	66.9 (27.2)	63.8 (30.8)	65.8 (23.9)	71.8 (30.3)	65.2 (22.1)	0.030
COWAT Composite (# words)	42.0 (11.9)	42.4 (11.0)	41.9 (12.7)	40.5 (11.5)	43.2 (12.4)	0.153
DVT Errors (#)	8.1 (8.2)	7.5 (9.6)	9.0 (7.7)	7.9 (7.6)	8.0 (7.8)	0.427
DVT Time (sec)	377.0 (84.1)	369.0 (82.2)	374.8 (83.7)	387.9 (86.5)	374.5 (83.1)	0.190
Stroop Word (#)	70.4 (13.1)	71.2 (13.6)	71.8 (13.5)	68.1 (12.8)	71.1 (12.4)	0.038
Stroop Color (#)	97.8 (17.6)	100.3 (17.3)	96.5 (18.7)	95.3 (17.8)	99.3 (16.5)	0.032
Stroop Color-Word (#)	38.1 (9.0)	38.7 (9.5)	38.0 (8.7)	37.1 (9.1)	38.6 (8.9)	0.337

Table 2. Means and Standard Deviations (in Parentheses) of the Three UFOV Subtests (Stimulus Identification, Divided Attention, and Selective Attention), the UFOV Composite, and the Blom Rank Transformed UFOV Composite at Randomization and at Post-Training.

Variable	Overall N=681	*Road Tour* On-Site No Boosters N=154	*Road Tour* On-Site With Boosters N=148	Attention Control On-Site N=188	*Road Tour* At-Home N=191	*p* value
Randomization						
Stimulus Identification	21.5 (20. 8)	19.6 (9.2)	22.7 (25.5)	24.4 (29.6)	21.5 (20.8)	0.057
Divided Attention	75.2 (89.8)	79.1 (98.9)	65.9 (70.2)	81.4 (94.6)	73.4 (90.9)	0.421
Selective Attention	203.3 (103.1)	202.5 (106.3)	193.7 (94.7)	214.1 (108.5)	200.7 (101.0)	0.331
UFOV Composite	300.0 (181.6)	301.2 (192.5)	282.7 (154.9)	319.9 (197.1)	292.8 (175.3)	0.277
Blom Rank Transformed UFOV Composite	0.0 (1.0)	-0.0 (1.0)	-0.1 (0.9)	0.1 (1.0)	-0.0 (1.0)	0.395
Post-Training	Overall N=620	*Road Tour* On-Site No Boosters N=138	*Road Tour* On-Site With Boosters N=142	Attention Control On-Site N=176	*Road Tour* At-Home N=172	*p* value
Stimulus Identification	18.5 (10.8)	17.7 (5.8)	17.3 (4.4)	20.8 (17.5)	17.9 (7.8)	0.011
Divided Attention	45.4 (66.9)	37.6 (50.3)	44.7 (64.0)	63.1 (89.9)	34.3 (47.4)	0.001
Selective Attention	157.5 (93.0)	135.1 (75.9)	149.1 (87.8)	201.6 (106.6)	136.9 (79.0)	0.001
UFOV Composite	221.6 (147.2)	190.5 (114.0)	211.6 (137.6)	285.5 (182.4)	189.1 (114.8)	0.001
Blom Rank Transformed UFOV Composite	0.0 (0.8)	-0.1 (0.7)	-0.0 (0.9)	0.4 (0.8)	-0.2 (0.8)	0.001

Table 3. Pooled and Age-Stratum Specific Multiple Linear Regression Results for Predicting the Blom Rank transformed Composite UFOV Score at 6-8 Weeks Post-Randomization.

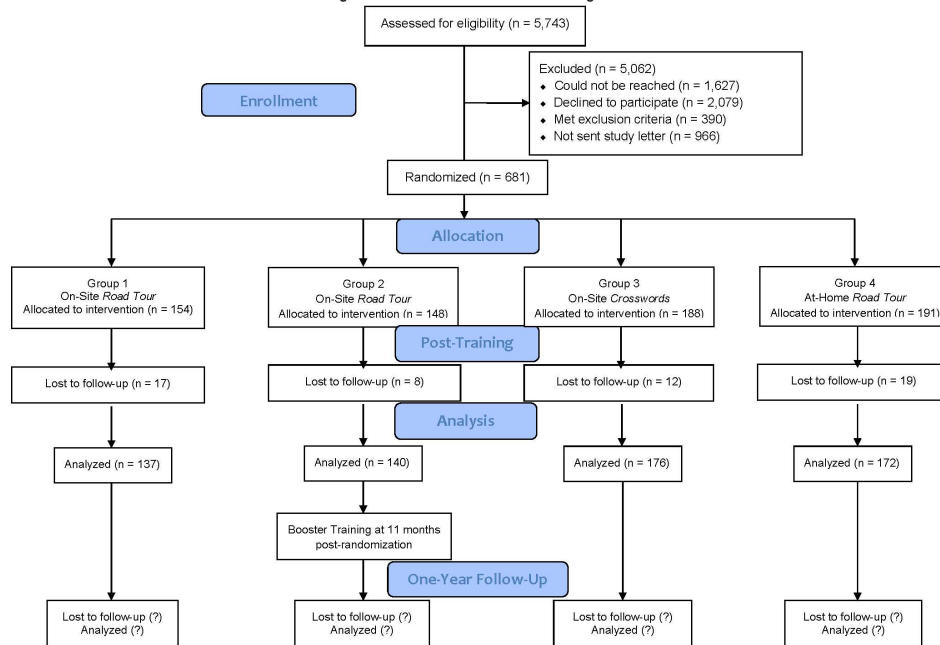|	Unstandardized Regression Coefficient *b*	*P* value	Lower $CI_{95\%}$	Higher $CI_{95\%}$
Pooled Analysis with Both Age Strata (N = 620)				
Intercept	0.415	0.001	0.309	0.520
Any *Road Tour* Training (N=444)	0.558	0.001	-0.433	-0.683
Onsite Attention Control (N=176)	0.000	---	---	---
Blom Rank Transformed UFOV at Randomization	0.643	0.001	0.585	0.700
R Squared	0.491	0.001		
Separate Analysis in the ≥ 65 Age Stratum (N = 209)				
Intercept	0.518	0.001	0.343	0.694
Any *Road Tour* Training (N=154)	-0.479	0.001	-0.290	-0.668
Onsite Attention Control (N=55)	0.000	---	---	---
Blom Rank Transformed UFOV at Randomization	0.650	0.001	0.547	0.754
R Squared	0.482	0.001		
Separate Analysis in the 50-64 Age Stratum (N = 411)				
Intercept	0.352	0.001	0.218	0.486
Any *Road Tour* Training (N=292)	-0.626	0.001	-0.467	-0.785
Onsite Attention Control (N=119)	0.000	---	---	---
Blom Rank Transformed UFOV at Randomization	0.556	0.001	0.479	0.634
R Squared	0.413	0.001		

Table 4. Pooled and Age-Stratum Specific Multiple Linear Regression Results for Predicting the Blom Rank transformed Composite UFOV Score at 6-8 Weeks Post-Randomization.

	Unstandardized Regression Coefficient b	P value	Lower $CI_{95\%}$	Higher $CI_{95\%}$
Pooled Analysis with Both Age Strata (N = 620)				
Intercept	0.415	0.001	0.309	0.520
Road Tour Onsite no Boosters (N=139)	-0.457	0.001	-0.299	-0.616
Road Tour Onsite with Boosters (N=136)	-0.585	0.001	-0.426	-0.745
Onsite Attention Control (N=174)	0.000	---	---	---
Road Tour At Home (N=171)	-0.629	0.001	-0.469	-0.769
Blom Rank Transformed UFOV at Randomization	0.642	0.001	0.585	0.699
R Squared	0.495	0.001		
Separate Analysis in the $\geq$ 65 Age Stratum (N = 209)				
Intercept	0.520	0.001	0.343	0.697
Road Tour Onsite no Boosters (N=47)	-0.465	0.001	-0.226	-0.704
Road Tour Onsite with Boosters (N=46)	-0.480	0.001	-0.240	-0.721
Onsite Attention Control (N=55)	0.000	---	---	---
Road Tour At Home (N=61)	-0.490	0.001	-0.263	-0.718
Blom Rank Transformed UFOV at Randomization	0.648	0.001	0.542	0.697
R Squared	0.482	0.001		
Separate Analysis in the 50-64 Age Stratum (N = 411)				
Intercept	0.353	0.001	0.219	0.486
Road Tour Onsite no Boosters (N=92)	-0.483	0.001	-0.280	-0.685
Road Tour Onsite with Boosters (N=90)	-0.665	0.001	-0.462	-0.869
Onsite Attention Control (N=119)	0.000	---	---	---
Road Tour At Home (N=110)	-0.711	0.001	-0.519	-0.903
Blom Rank Transformed UFOV at Randomization	0.560	0.001	0.483	0.638
R Squared	0.421	0.001		

Figure 1. IHAMS CONSORT Flow Diagram.

Assessed for eligibility (n = 5,743)

Enrollment

Excluded (n = 5,062)
- Could not be reached (n = 1,627)
- Declined to participate (n = 2,079)
- Met exclusion criteria (n = 390)
- Not sent study letter (n = 966)

Randomized (n = 681)

Allocation

Group 1
On-Site *Road Tour*
Allocated to intervention (n = 154)

Group 2
On-Site *Road Tour*
Allocated to intervention (n = 148)

Group 3
On-Site *Crosswords*
Allocated to intervention (n = 188)

Group 4
At-Home *Road Tour*
Allocated to intervention (n = 191)

Post-Training

Lost to follow-up (n = 17)

Lost to follow-up (n = 8)

Lost to follow-up (n = 12)

Lost to follow-up (n = 19)

Analysis

Analyzed (n = 137)

Analyzed (n = 140)

Analyzed (n = 176)

Analyzed (n = 172)

Booster Training at 11 months post-randomization

One-Year Follow-Up

Lost to follow-up (?)
Analyzed (?)

Lost to follow-up (?)
Analyzed (?)

Lost to follow-up (?)
Analyzed (?)

Lost to follow-up (?)
Analyzed (?)

279x215mm (200 x 200 DPI)

282x211mm (288 x 288 DPI)

282x211mm (288 x 288 DPI)

282x211mm (288 x 288 DPI)

282x211mm (288 x 288 DPI)

282x211mm (288 x 288 DPI)

282x211mm (288 x 288 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and	2a	Scientific background and explanation of rationale	5-7
objectives	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6-7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	na
Participants	4a	Eligibility criteria for participants	8-9
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-8, 11-12
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	na
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	na
Randomisation:			
Sequence	8a	Method used to generate the random allocation sequence	9-10
generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)	9-10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9-10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9-10
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	9-10

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	7-8, 11-12
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12-13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12-13
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	32
	13b	For each group, losses and exclusions after randomisation, together with reasons	32
Recruitment	14a	Dates defining the periods of recruitment and follow-up	9
	14b	Why the trial ended or was stopped	na
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	34-35
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	32
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	15-18, 37-38
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	15-18, 37-38
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	14-15
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	na
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	23
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	23
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	19-22
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	7, ref. 25
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	24

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.