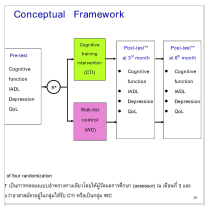

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Feb 08, 2022

The effects of cognitive training in healthy community residing Thai elderly: randomized controlled trial V.1

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protocol .

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The authors declare that they have no conflicts of interest.

Aim: Cognitive training intervention (CTI) in the elderly is associated with a risk reduction of dementia; however, the effects of interactive computerized-CTI in old ages have been inconclusive. The present study aimed to determine the effects of low-technology CTI in community-based populations.

Methods: The study was a 2-arm parallel single-blinded randomized controlled intervention trial. The primary endpoint assessed the treatment effect by examination of global cognitive function, utilizing the Thai Mental State Examination (TMSE), at the 12th week (T1), while the secondary endpoint evaluated the carry-over effect at the 24th week (T2).

Results: Eighty-six eligible participants were recruited from a senior society on the edge of Bangkok. At baseline (T0), the mean age and TMSE score among CTI (n=44) and wait-list (n=42) groups were similar (age; 66.66±5.52 and 67.52±6.46; TMSE; 28.84±1.38 and 28.83±1.12, respectively). For the CTI group, the mean number of cognitive training sessions was 14.82±7.62. By using intention-to-treat analysis at the primary endpoint, the mean difference score of TMSE in the CTI groups was significantly higher than the wait-list group (ΔTMSEbetween group at T1-T0=0.57; 95%CI=0.07 to 1.08.; p = 0.026) while the effect size was 0.48. At the secondary endpoint, there was no significant difference observed between the CTI and wait-list groups (ΔTMSEbetween group at T2-T0=0.33; 95%CI= -0.23 to 0.88; p = 0.248) while the effect size was 0.25.

Conclusions: CTI showed a significant treatment effect for improvement in global cognitive function in healthy Thai elderly but did not demonstrate a carryover effect.

ProtocolRCTCogTrainEng_PLOSONE.pdf

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cognitive functions, community, elderly, healthy, randomized controlled trial

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The cognitive training intervention (CTI) is referred to as a non-pharmacological intervention that involves a kind of restorative strategy to improve cognitive performance in the healthy elderly. The exercises in the CTI for this study combined six cognitive functions (i.e. complex attention, executive function, learning and memory, language, visuoconstruction-perceptual ability, and social cognition). The CTI was implemented twice per week with 30 minutes allocated to each session (24 sessions in 12 weeks). The sessions were led by the author who guided the participants through each activity systematically. Each session comprised eight three-minute sections and followed the same format: 1) check-in and introduction, 2) cognitive domain practices (6 sections), and 3) summary and feedback section. There was a one-minute break after each section to enable participants to recover. The CTI was run by an audio-visual digital video disk created by the authors which explained instruction and demonstration in each lesson and involved an individual paper-pencil workbook. The CTI employed speed tests, matching activities, gap completion, and short-answer questions.

1. Materials for primary outcome

The primary outcome was the evaluation of global cognitive function with the use of Thai Mental Status Examination (TMSE)[12], of which total score is 30 and is divided into six categories: orientation (score of 6), registration (3), attention (5), calculation (3), language (10), and recall (3). The average total score among Thai elderlies (60-70 years old) who are free from underlying diseases and psychoactive substances is 27.38±2.02. According to this examination, elderlies who scored higher than 23 were considered normal.

2. Materials for secondary outcome

The secondary outcome consisted of three components:

2.1 Evaluation of cognitive function was performed in merely five from the total of six subdomains by using a neuropsychological assessment battery.

- Attention-concentration with Digit Span Forward
- Working memory with Digit Span Backward
- Secondary verbal memory with Word List Learning in Alzheimer's Disease Assessment Scale — cognitive subscale (ADAS-cog)13
- Psychomotor speed with Trail-Making Test A
- Executive function with Trail-Making Test B
- Delayed recall memory with Word Recall in Alzheimer's Disease Assessment Scale — cognitive subscale (ADAS-cog)[13]
- Visuoconstructional-perceptional ability with Constructional praxis in Alzheimer's Disease Assessment Scale — cognitive subscale (ADAS-cog)
- Language fluency with Letter and Category Fluency Test

2.2 Assessment of Elderlies' Quality of Life was composed of

- Thai Geriatric Depression Scale-15 (TGDS-15)
- Older People's Quality of Life Questionnaire (OPQOL-Brief)

References

References.pdf

No safety warnings

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The authors declare that they have no conflicts of interest.

- Target Population

Thai elderly people with the minimum age of 55 years in the elderly center or the Center of the Development of Quality of Life for the Elderly who were not diagnosed with dementia or mild cognitive impairment (MCI)

- Population to be studied

Thai elderly people with the minimum age of 55 years in the elderly center or the Center of the Development of Quality of Life for the Elderly who were literate and not diagnosed

with dementia or MCI and participate in activities held by the elderly center.

- Sample
Thai elderly people with the minimum age of 55 years who joined activities at the elderly center showed interest and willingness in being part of the study. Criteria for sample selection are as follows.

Inclusion criteria
1. Those who are ≥ 55 years old.
2. Those who are members of the elderly center/ club.
3. Those who show a willingness to participate in the study.

Exclusion criteria
1. Those whose education level is lower than six years of education.
2. Those who have a visual disorder cannot see with glasses on.
3. Those who even with hearing aids have hearing difficulties that impair their communication.
4. Those who have been a member of the elderly center/ club for shorter than three months.
5. Those who have compromised intellect and possess the Thai Mental Status Examination (TMSE)8 score of < 24.
6. Those who are diagnosed with dementia based on DSM-54 and the National Institute on Aging5 and have Clinical Dementia Rating Scale (CDR) ≥ 1.
7. Those who are diagnosed with MCI based on DSM-54 and the National Institute on Aging7 and have Clinical Dementia Rating Scale (CDR) of 0.5.
8. Those who are currently diagnosed with all substance use disorders except tobacco and caffeine use disorder based on DSM-5.
9. Those who are diagnosed with neurological disorders are stroke, epilepsy, and Parkinson's disease.
10. Those who are diagnosed with major psychiatric disorders, for instance, psychotic disorders, bipolar disorders, and major depressive disorders are based on DSM-5.
11. Those who use benzodiazepine every day
12. Those who use anticholinergics every day
13. Those who use Acetylcholinesterase inhibitor (AChEI) every day.
14. Those who use N-methyl D-aspartate (NMDA) receptor antagonists every day.

Criteria for Setting
Eligible participants were recruited at the Senior Society of Nonthaburi Municipality, Bangkok, Thailand due to its following qualities:
1. It was a place established to improve the quality of life and promote the career of the Thai elderly.
2. It was located in the area of Bangkok Metropolitan or its vicinity.
3. It had approximately 200 members who were at least sixty years old. This number was

sufficient for the volunteer recruitment in this study. (Based on the participation rate at 50%)
4. It had an activity room that could accommodate at least 50 people.

- Sample size
The sample size was estimated using a 1:1 ratio 2–sample parallel RCT with a continuous outcome.
The statistical significance level of $\alpha = 0.05$
The power (β) was set at 0.80
When values were substituted in the formula, μ_con, the mean of TMSE in normal elderlies obtained from the literature review, was 27.80 and σ was 1.57.
The effect size was set at 1.0 (difference of the mean of TMSE between the treatment and control group). According to this formula, the number of each arm was 39; however, the author prevented the loss of follow-ups on the participants by increasing the sample size by 10 percent. As a result, the final sample size per arm was 44.

1. Materials for primary outcome
The primary outcome was the evaluation of global cognitive function with the use of the Thai Mental Status Examination (TMSE), of which total score is 30 and is divided into six categories: orientation (score of 6), registration (3), attention (5), calculation (3), language (10), and recall (3). The average total score among Thai elderlies (60-70 years old) who are free from underlying diseases and psychoactive substances is 27.38±2.02. According to this examination, elderlies who scored higher than 23 were considered normal.

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The secondary outcome consisted of three components:
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- Attention-concentration with Digit Span Forward
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- Language fluency with Letter and Category Fluency Test
2.2 Assessment of Elderlies' Quality of Life was composed of
- Thai Geriatric Depression Scale-15 (TGDS-15)
- Older People's Quality of Life Questionnaire (OPQOL-Brief)

- Identification of the Study End Point

This project lasted 24 weeks (6 months) with two points of time when the outcome was investigated.
1. In the 12th week of the study, when the participants in the control group received their last CTs, both primary and secondary outcomes were measured to point out their immediate effect.
2. In the 24th week when the participants in the treatment group received their last CT, both primary and secondary outcomes are examined to see it sustain effect of CT. However, between the 12th and the 24th week, no CTs were arranged.

– Statistical method
1. Data analysis with descriptive statistics was implemented to analyze the participants' personal data, which were frequency and percent. In case the data showed normal distribution, mean, standard deviation (SD), 95% confidence interval (95% CI) were applied; whereas when the data were irregularly distributed, median and interquartile range (IQR) were used instead.
2. Comparative analysis of primary outcome and secondary outcome in the treatment and control group was carried out using an independent sample t-test because the study aimed to measure the resulting mean of the cognitive function of the two groups: the treatment group who received CT and the wait-list control group.
3. The comparison between the primary and secondary results was performed twice, in the third and sixth month, to examine the treatment effect (immediate effect) and carryover effect (sustained effect) respectively.
4. When some participants terminated their participation or missed their follow-ups or appointments, Intention- To-Treat (ITT) analysis was carried out in comparison with Per-Protocol analysis (PP) based on the data of all participants who passed the screening and were selected as the control group regardless of their study protocol completion.

Study design

1 - 1:1 ratio 2-arm parallel single-blinded intervention randomized controlled trial study design (RCT) with a single-blinded assessor.
- All cognitive function outcomes were assessed by trained blinded psychologists not involved in the recruitment process and experimental phase.
- Study Endpoint Classification: Efficacy Study
- Intervention Model: Parallel
- -Number of Arms: 2

1.1 **Allocation**
- Randomized controlled trial, Block of four techniques

1.2 **Arm 1**
- Intervention Name: Cognitive training program + unstructured recreational group activities
- Type: Experimental
- Classification: Behavioral- Descriptions: The CTI referred to a non-

pharmacological intervention that involved a kind of restorative strategy to improve cognitive performance in healthy elderly. The exercises in the CTI for this study combined 6 cognitive functions (i.e. complex attention, executive function, learning and memory, language, visuoconstruction-perceptual ability, and social cognition). The CTI was implemented twice per week with 30 minutes allocated to each session (24 sessions in 12 weeks).The sessions were led by the author who guided the participants through each activity systematically.Each session comprised of 8 sections of 3-minutes each following the same format:1) check-in and introduction, 2) cognitive domain practices (6 sections), and 3) summary and feedback section. There was a 1-minute break after each section ended to enable participants to recover. The CTI was run by an audio-visual digital video disk created by the authors which explained instruction and demonstration in each lesson and involved an individual paper-pencil workbook. The CTI employed speed tests, matching activities, gap completion, and short-answer questions.

1.3 Arm 2

- Intervention Name: Wait-list group
- Type: Unstructured recreational group activities
- Classification: Behavioral
- Descriptions: Wait-list groups voluntarily attended additional activities following a regular schedule at the elderly center such as aerobic exercises, ballroom dance, folk Thai dance, fitness drills, yoga, Tai Chi, Karaoke, musical instrument lessons, Mandarin-Chinese or English lessons, and practice with dharma and meditation.

1.4 Objectives/ Hypothesis/ Assumption

Primary objective: To investigate how cognitive training intervention affects cognitive function in the elderly with normal cognitive function.

Hypothesis: The elderly whose cognitive function is normal and undergoes cognitive training possess more competent cognitive function performance than those with normal cognitive function but receive no cognitive training.

Assumption:

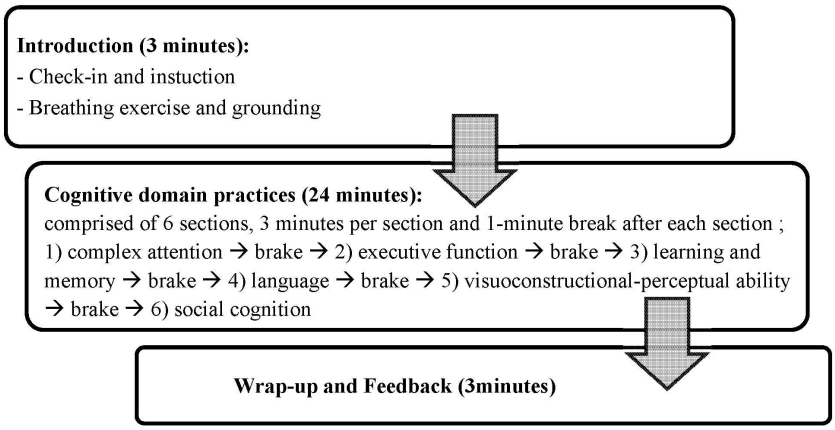
1. All participants understand and sincerely answer all questions.
2. The present study determines that a cognitive training program (CT) is the only available restorative strategy.

2 -Investigational product, dosage & route of administration

The CTI is referred to as a non-pharmacological intervention that involves a kind of restorative strategy to improve cognitive performance in the healthy elderly. The exercises in the CTI for this study combined six cognitive functions (i.e., complex attention, executive function, learning and memory, language, visuoconstruction-perceptual ability, and social cognition). The CTI was implemented twice per week with 30 minutes allocated to each session (24 sessions in 12 weeks).The sessions were led by the author who guided the participants through each activity systematically.Each session comprised eight three-minute sections and followed the same format:1) check-in and introduction, 2) cognitive domain practices (6 sections), and 3) summary and feedback section. There was a one-

minute break after each section to enable participants to recover. The CTI was run by an audio-visual digital video disk created by the authors which explained instruction and demonstration in each lesson and involved an individual paper-pencil workbook. The CTI employed speed tests, matching activities, gap completion, and short-answer questions.
-Comparator, dosage & mode of administration
The comparator was the participants in the control group who were also in the wait-list control group. While on the waitlist, the participants in the control group were still able to join all the activities held by the elderly club.

Figure 2. Cognitive Training Intervention (CTI) Protocol



3 Sample size

The sample size was estimated using a 1:1 ratio 2–sample parallel RCT with the continuous outcome; 2 tailed test.
The statistical significance level of α = 0.05
The power (β) was set at 0.80
When values were substituted in the formula, the mean of TMSE in normal elderlies obtained from the literature review, was 27.80 and SD was 1.57.
The effect size was set at 1.0 (difference of the mean of TMSE between the treatment and control group). According to this formula, the number of each arm was 39; however, the author prevented the loss of follow-ups on the participants by increasing the sample size by 10 percent. As a result, the final sample size per arm was 44.

4 Conceptual Framework

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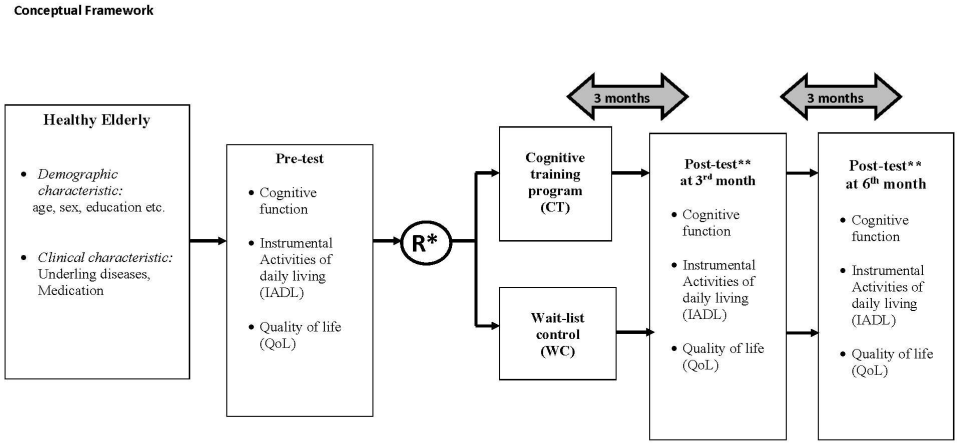
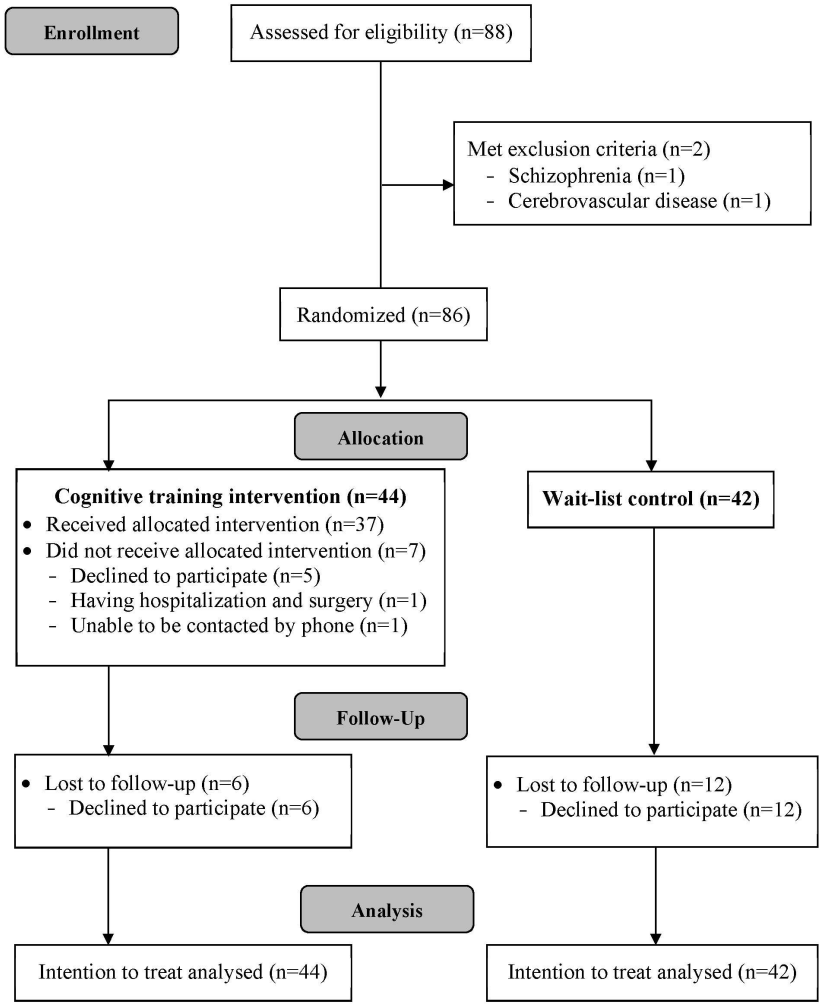


Remark * R, Block of four randomization; ** 1:1 ratio 2-arm parallel single-blinded intervention RCT (All cognitive function outcomes were assessed by trained blinded psychologists not involved in the recruitment process and experimental phase.)

Enrollment

5 Assessed for eligibility

Figure 1. Flow diagram of randomization



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8.Those who are currently diagnosed with all substance use disorders except tobacco and caffeine use disorder based on DSM-5[9,10].
9.Those who are diagnosed with neurological disorders are stroke, epilepsy, and Parkinson's disease.
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3.It had approximately 200 members who were at least sixty years old. This number was sufficient for the volunteer recruitment in this study. (Based on the participation rate at 50%)
4.It had an activity room that could accommodate at least 50 people.

Expected results

6 Expected results

In this research study, two outcomes were identified: primary and secondary outcome with the use of several tools as follows.

6.1 -Primary outcome

The primary outcome was the evaluation of global cognitive function with the use of Thai Mental Status Examination (TMSE), of which total score is 30 and is divided into six categories: orientation (score of 6), registration (3), attention (5), calculation (3), language (10), and recall (3). The average total score among Thai elderlies (60-70 years old) who are free from underlying diseases and psychoactive substances is 27.38±2.02. According to this examination,

elderlies who scored higher than 23 were considered normal.

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The secondary outcome consisted of three components:
1.Evaluation of cognitive function was performed in merely five from the total of six subdomains by using a neuropsychological assessment battery.
1.1 Attention-concentration with digit Span Forward
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1.3 Secondary verbal memory with word List Learning in Alzheimer's Disease Assessment Scale — cognitive subscale (ADAS-cog)
1.4Psychomotor speed with trail-Making Test A
1.5 Executive function with trail-Making Test B
1.6 Delayed recall memory with word Recall in Alzheimer's Disease Assessment Scale — cognitive subscale (ADAS-cog)
1.7 Visuoconstructional-perceptional ability with Constructional praxis in Alzheimer's Disease Assessment Scale — cognitive subscale (ADAS-cog)
1.8 Language fluency with letter and Category Fluency Test

6.3 **Assessment of Elderlies' Quality of Life** was composed of

- Thai Geriatric Depression Scale-15 (TGDS-15)
- Older People's Quality of Life Questionnaire (OPQOL-Brief)

7 Identification of the Study End Point

This project lasted 24 weeks (6 months) with two points of time when the outcome was investigated.
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2. In the 24^{th} week when the participants in the treatment group received their last CT, both primary and secondary outcomes are examined to see it sustain effect of CT. However, between the 12^{th} and the 24^{th}week, no CTs were arranged.

Experimental period 12w

8

37

ตารางที่ 2 ขั้นตอนการดำเนินการศึกษาทดลอง

Visit ที่ 1; Wk ที่ 0	Pre-test ได้แก่ TMSE, L-IADL, TGDS และ OPQOL-Brief		
Randomization			
เริ่มการทดลอง	กลุ่ม Intervention		กลุ่ม Control
Visit ที่ 2; Wk ที่ 1	CTI		WC
Visit ที่ 3; Wk ที่ 1	CTI		WC
Visit ที่ 4; Wk ที่ 2	CTI		WC
Visit ที่ 5; Wk ที่ 2	CTI		WC
Visit ที่ 6; Wk ที่ 3	CTI		WC
Visit ที่ 7; Wk ที่ 3	CTI		WC
Visit ที่ 8; Wk ที่ 4	CTI		WC
Visit ที่ 9; Wk ที่ 4	CTI		WC
Visit ที่ 10; Wk ที่ 5	CTI		WC
Visit ที่ 11; Wk ที่ 5	CTI		WC
Visit ที่ 12; Wk ที่ 6	CTI		WC
Visit ที่ 13; Wk ที่ 6	CTI		WC
Visit ที่ 14; Wk ที่ 7	CTI		WC
Visit ที่ 15; Wk ที่ 7	CTI		WC
Visit ที่ 16; Wk ที่ 8	CTI		WC
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Visit ที่ 20; Wk ที่ 10	CTI		WC
Visit ที่ 21; Wk ที่ 10	CTI		WC
Visit ที่ 22; Wk ที่ 11	CTI		WC
Visit ที่ 23; Wk ที่ 11	CTI		WC
Visit ที่ 24; Wk ที่ 12	CTI		WC
Visit ที่ 25; Wk ที่ 12	CTI		WC
Visit ที่ 26; Wk ที่ 12	1st End Point TMSE, Neuropsychological assessment, TGDS และ OPQOL-Brief		
ระหว่าง Wk ที่ 13 – 23	ไม่ได้รับ CTI แต่เข้าร่วมกิจกรรมในชมรมผู้สูงอายุตามปกติ		เข้าร่วมกิจกรรมในชมรมผู้สูงอายุตามปกติ
Visit ที่ 27; Wk ที่ 24	2nd End Point TMSE, Neuropsychological assessment, TGDS และ OPQOL-Brief		
End			

หมายเหตุ CTI = Cognitive training intervention;
WC = Wait-list control เข้าร่วมกิจกรรมในชมรมผู้สูงอายุตามปกติระหว่างสัปดาห์ที่ 1-12

Step 8 includes a Step case.

Experimental Group

Wait list control