The efficacy of computerized cognitive training in patients with coronary heart disease and cognitive impairment, no dementia: a randomized controlled trial（COG-T CHD）

A multicenter, double-blind, 1:1 parallel grouped RCT

Comparing the effects of computerized cognitive training Versus positive controls

Statistical Analysis Plan

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1. Administration information

TRIAL FULL TITLE	The efficacy of computerized cognitive training in patients with coronary heart disease and cognitive impairment, no dementia: a randomized controlled trial（COG-T CHD）
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SAP AUTHOR(s)	Yi Ye, Ruixuan Li, Qing Chen

1.1 Approvals

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) topic E9 Statistical Principles for Clinical Trials. In particular, we confirm that analysis plan was developed in a completely blinded manner, that is without knowledge of the effect of the intervention(s) being assessed.

Name	Signature	Date
Changsheng Ma		January 20, 2024
Yong Zeng		January 20, 2024

2. **Study overview**

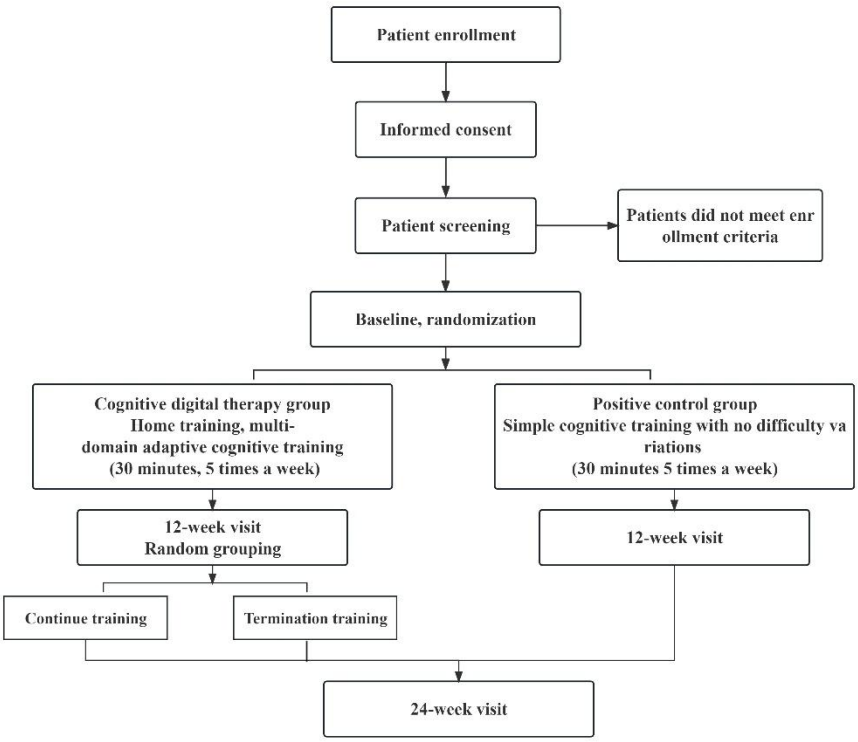
The objective of the COG-T CHD study is to determine the efficacy of computerized cognitive training on global cognitive function in patients with CHD and cognitive impairment compared with positive controls, over a 12-week training period. At the same time, we will continue the follow-up until week 24 to determine whether the effects of the intervention are sustained and investigate the changes of head MRI structure and function in the computerized cognitive training group and the positive control group were observed at week 12/24.

2.1 Study design

This study was a multicentre, double-blind, parallel randomized controlled study using a 1:1 parallel control design. A total of 200 patients with coronary heart disease combined with cognitive decline but no dementia will be enrolled from 8 centres (Beijing Anzhen Hospital affiliated to Capital Medical University, Peking University Third Hospital, The second hospital of Chifeng, The First Affiliated Hospital of Hebei North University, Handan Central Hospital, The First Hospital of Hebei Medical University, Beijing Sixth Hospital, Inner Mongolia Ordos Central Hospital Kangbashi Department). All patients were stratified and randomly assigned to the cognitive digital therapy group and the positive control group according to age and educational level, and were given cognitive training at least 5 times a

week for at least 30 minutes each time for a total of 12 weeks. All subjects were interviewed at 12 weeks. After completing the 12-week visit, the researchers will unblind the subjects, the positive control group will end the intervention, and the cognitive digital therapy group will repeat the intervention 1:1 randomization: One group ended the cognitive training, and the other group continued the training until 24 weeks. Each patient will be followed up to 24 weeks. The primary outcome was the proportion of improvement in overall cognitive function at 12 weeks, defined as 0.67 standard deviation（SD）above baseline cognitive function as measured by the Basic Cognitive Ability Test (BCAT). （see Fig. 1）

Fig. 1 Participant flow through study



2.2 Intervention Description

A total of 200 patients were randomly divided into the following two groups according to age (≥75 years old, <75 years old) and education level (completion of junior high school and below, senior high school and above) :(1) cognitive digital therapy group; (2) Positive control group.

Cognitive digital therapy group

The patients in the cognitive digital therapy group were trained in multi-dimensional cognitive function, including attention, memory, executive function, thinking, processing speed and perception. The system will adaptively adjust the training difficulty and training plan according to the patient's current training time and training results, and train the patient's weak cognitive ability as much as possible. The patients had the same total amount of training per day.

Positive control group

The training content of the positive control group was cognitive training tasks with weak difficulty or no difficulty change. The patients underwent cognitive function training with a fixed program, including 15 training items, and the internal difficulty of the training items remained constant. The system presents the training content randomly according to the training scheme. The patients had the same total amount of training per day.

2.3 Sample size calculation

The sample size was calculated based on previous studies[1] and the following assumptions （see Fig. 2）:

1. After 12 weeks of intervention, 30% of patients in the cognitive digital therapy group improved their overall cognitive scores (0.67SD);

2. The overall cognitive score of positive control group was improved by 10%;

3. Bilateral test (α=0.05) was adopted, the minimum efficacy of the test was 90%, the 3-month loss rate was assumed to be 20%, the sample size was calculated N=198, and 200 patients were finally included.

Fig. 2: Sample size

Dropout-Inflated Sample Size

	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
Dropout Rate	N1	N2	N	N1'	N2'	N'	D1	D2	D
20%	79	79	158	99	99	198	20	20	40

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2.4 Aims and objectives

To determine the effectiveness of the computerized cognitive training on the overall cognitivefunction in patients with CHD and cognitive impairment without dementia, compared to positive controls, over a 12-week training.

2.5 Outcomes

2.5.1 Primary outcome

The primary endpoint of the study will be the proportion of subjects with improved global cognitive function at 12 weeks. As described in section 2.3, the cognitive function will be evaluated by BCAT. The BCAT will include four distinct brain functions, namely processing speed, working memory, episodic memory and visuospatial. The global cognitive function score will be calculated as the average of scores across each cognitive domain. In the DELIGHT trial, clinically significant improvement in cognitive function was defined as a Z-value of the overall BCAT score that was 0.67 SD (2 points of task score) higher than the baseline Z-value after 12 weeks training. The Z-value for each cognitive domain can be obtained by referring to the Z score conversion table (Table.1.2).

Table 1. The correspondence between BCAT cognitive ability scores and Z-scores	
BCAT score	Z-score
19	3.00 (2.83 ~ 3.17)
18	2.67 (2.50 ~ 2.83)
17	2.33 (2.17 ~ 2.50)
16	2.00 (1.83 ~ 2.17)
15	1.67 (1.50 ~ 1.83)
14	1.33 (1.17 ~ 1.50)
13	1.00 (0.83 ~ 1.17)
12	0.67 (0.50 ~ 0.83)
11	0.33 (0.17 ~ 0.50)
10	0.00 (-0.17 ~ 0.17)
9	-0.33 (-0.50 ~ -0.17)
8	-0.67 (-0.83 ~ -0.5)
7	-1.00 (-1.17 ~ -0.83)
6	-1.33 (-1.50 ~ -1.17)
5	-1.67 (-1.83 ~ -1.50)
4	-2.00 (-2.17 ~ -1.83)
3	-2.33 (-2.50 ~ -2.17)
2	-2.67 (-2.83 ~ -2.50)
1	-3.00 (-3.17 ~ -2.83)

Table 2. Threshold for basic cognitive impairment in different age groups based on BCAT

	18-29 years old	30-39 years old	40-49 years old	50-59 years old	60-59 years old	Over 70 years old
processing speed	-0.16	-0.43	-0.69	-1.09	-1.39	-1.71
working memory	-0.25	-0.45	-0.74	-1.01	-1.26	-1.43
episodic memory	-0.34	-0.52	-0.80	-1.07	-1.20	-1.47
visual space	-0.53	-0.69	-0.76	-0.90	-1.05	-1.22

2.5.2 Secondary outcomes

1) The proportion of clinically significant improvement (2 points of task score) in global cognitive function from baseline at 24 weeks;

2) The proportion of improvement in cognitive function from baseline in each cognitive domain at 12 weeks and 24 weeks;

3) Changes in global cognitive function scores in the intervention group compared to the control group from baseline to week 12 and 24;

4) Changes in subjects' self-efficacy scores from baseline to 12 weeks and 24 weeks; Self-Efficacy scores was measured by the Chinese version of the General self-efficacy Scale-Schwarzer (GSES).

5) Changes in subjects' quality of life scores from baseline to12 weeks and 24 weeks; Quality of life scores was measured using the European Five-Dimensional Health Scale (EQ- 5D-3L).

6) Changes in subjects' anxiety and depression scores from baseline to 12 weeks and 24

weeks. Anxiety-depression status was measured by the Subject Health Questionnaire: Depression Scale (PHQ-9)[2] and the Generalized Anxiety Scale (GAD-7)[3].

2.5.3 Exploratory outcome

Changes in structural and functional characteristics of brain MRI will be evaluated at week 12/24 compared to baseline. Consented participants will undergo 3.0T MRI imaging to assess changes in head MRI structure and function before and after cognitive training.

3. Population and subgroups to be analyzed

The full analytical population included all randomized subject who completed the baseline assessment and took at least 1 intervention session, regardless of their adherence to the rest intervention. This analytical population set following the modified intention to treat analysis will be used for primary and secondary efficacy analysis.

4. Statistic

4.1 General analysis considerations

The analyses will be conducted using SAS 9.4 statistical software. Descriptive statistics will be computed, including the sample size (n), means, standard deviations, medians, and inter and frequency counts and percentages for categorical variables. The efficacy endpoint will be summarized by assessment time points (baseline, 12, 24 weeks) and by intervention groups. Data will be examined for skewness and outliers. Categorical variables are shown as n (%), and continuous variables as mean (standard deviation [SD]) if normally distributed or median (interquartile range [IQR]) if there was a skew distribution. Shapiro-Wilktest will be used to test the normality, the data will be presented as a median (interquartile range) and transformed to approximate a normal distribution. If transformation is not feasible, a

Wilcoxon test can be performed.

The following descriptive data will be present by intervention groups:

Demography characteristics:

Gender(female%), Age(n), Education level (middle school or below, high school or above)

Laboratory measure(n):

BMI, Pulse, Blood pressure (baseline,12 weeks and 24 weeks), Blood test (FBG, TG, etc.), Electrocardiogram result (sinus rhythm/other), Doppler echocardiography (LVEF, etc.)

Medical/Cardiovascular disease history

Drug usage: Types of drugs and dosages

Self-reported disease/surgical history: Hypertension, Coronary artery disease, Coronary artery bypass/Stenting surgery, neurological disease etc.

4.2 Timing of analysis

The data clearance and analysis will be initiated after all 200 participants finished their 24-week visiting.

4.3 Discontinuing/Intervention Deviation

Given the intervention's nature, the study will not result in any foreseeable harm or an objective need to stop the intervention. The patient will be informed that he or she may request a suspension of training or withdrawal from the study at any time for any reason and

that this will not affect his or her routine medical treatment. If the withdraw occurs, the existing data will be retained and the subsequent data will be marked as missing data. This study defines missing follow-up as an uncertain primary outcome in randomized participants. If a participant fails to return to the clinic for a scheduled study visit, the site must make every effort to reconnect with the participants in certain window. In general, retrospective visits are not permitted. However, the adverse measure will still be recorded and involved.

There are no plans to modify the assigned intervention. If adverse events occur, investigators will determine whether continued intervention is harmful to the safety or health of the participants, or sponsor requires participants to permanently stop the intervention, then the patient's intervention will be discontinued.

4.4 Efficacy analysis

4.4.1 Primary efficacy analyses

The null hypothesis H0 for the primary outcome will be there is no difference between in the proportion of patient demonstrated global cognitive function improvement in the cognitive training (intervention) group and the positive control group. The alternative hypothesis H1 will be the proportion in cognitive training group is different to the positive control group.

H0: $\mu x = \mu a$

H1: $\mu x \neq \mu a$

Where μx and μa represented the proportion of patients with BCAT score changes greater than 0.67SD from baseline to 12 weeks in the intervention and the control group,
respectively.

The proportion of subject with global cognitive function improvement in the intervention group will be compared to the proportion in the control group using Pearson chi-square test. The improvement in global cognitive function is defined as a 0.67SD increase in the overall BCAT test scores after 12 weeks training, when compared to the baseline scores. The estimated difference in proportion will be examined by using 95% confidence intervals for point estimations of endpoint occurrence probability. The proportion of subjects demonstrating improvement will be also analyzed for each subgroup, responding.

4.4.2 Main secondary efficacy analyses

The main secondary efficacy analyses will include comparison the intervention group and the control group for the 12-week endpoint analysis and three study groups after the re-randomization at 12 weeks, including the continue training group, stop training group and the control group at the baseline randomization, for the 24 weeks endpoint analysis. All statistical tests of the secondary analyses will be 2-sided, both 95% confidence intervals and p values will be reported.

1) The mean value of changes in scores of global cognitive functions from baseline to 12 weeks will be compared using independent t-test between the intervention group and control group. In cases any of domains' score not following normal distribution, if the transformation is not feasible, either the Wilcoxon test or Friedman M test will be used.

2) Difference in the proportion of improvement in global cognitive function after 24 weeks will be compared using Pearson chi-square test between continue training group and control group. Adjustment will be performed if necessary.

3) The mean value of changes in scores of global cognitive functions from baseline to 24 weeks will be compared using independent t-test between continue training group and control group. Adjustment will be performed if necessary.

4) The mean value of changes in scores of global cognitive functions from baseline to 24 weeks will be compared using independent t-test between the stop training group and control group. Adjustment will be performed if necessary.

4.4.3 Main exploratory efficacy analyses

All participants in this trial collected multimodal Magnetic resonance imaging (MRI) data including the structural MRI, resting-state functional MRI, Diffusion tensor imaging (DTI) and Arterial spin labeling (ASL) perfusion data. First, the preprocessing software such as SPM and FSL were used to preprocess the imaging data including the realignment, segmentation and registration of the brain images. Then the structural and functional changes brought by training were compared between two groups of participants. Moreover, the deep learning approaches were used to identify the neural signatures of cognitive impairment before and after the cognitive training in patients with coronary heart disease. Combining the neuropsychological scales, demographic information and biological indices, we further aimed to establish a unified predictive model of cognitive impairment and recovery encompassing the neurobiological correlates as well as impact of multiple potential covariates.

4.5 Subgroups

The following subgroups will be analysis in both primary and secondary outcomes to test the consistency:

Gender: female, or male;

Age: ≥70 years old, or < 70 years old at baseline visit;

Education: completion ofjunior high school and below, or senior high school and above

Anticoagulant usage: reporting using anticoagulant drugs in baseline assessment, or not

4.6 Sensitivity analysis

The ITT analysis and per-protocol analysis will also be employed as sensitivity analysis for the primary outcome.

4.7 Safety analysis

The occurrence of safety issues and serious adverse events during the implementation of this study is anticipated to be minimal. The participants will undergo regular monitoring for the following adverse events but no analysis is planned to perform.

Adverse Events (AE)

Adverse events (AE) are defined as undesirable symptoms, signs, diseases, or exacerbations of the above that occur during the study and may be related to the study. The determination of an adverse event should be based on a diagnostic or abnormal indicator. Events prior to randomization during the trial were not considered adverse events.

Serious Adverse Events (SAE)

In accordance with NHLBI and the OHRP Management Charter, a serious adverse event (SAE) is defined as meeting one of the following criteria:

1) resulting in fatality or posing a life-threatening risk;

2) causing severe and permanent disability;

3) requiring hospitalization or prolonged hospitalization;

4) leading to congenital abnormalities/birth defects in offspring;

5) being determined by investigator as a medical event that causes significant harm to the patient, necessitating medication or surgical intervention to prevent other conditions as outlined in the SAE (e.g., death, permanent disability, hospitalization).

4.8 Missing data

Missing data will be assumed missing completely at random. In general, no imputation will be applied unless otherwise specified. For subjects lost to follow-up or withdraw from thestudy, all available data prior to their loss of follow-up were included in the analysis.

4.9 Trial progress and actual sample size description

COG-T-CHD completed enrollment of all patients on November 17, 2023, with a total of 224 patients enrolled. We also updated the research progress information on ClinicalTrials. The actual sample size is larger than the calculated sample size, which is specifically explained here. During the initial implementation of the scheme, there were 32 subjects whose MRI data were not collected in the baseline period, which belonged to the scheme deviation. In order to ensure the integrity of the exploratory outcome indicators, 24 subjects were added to the original sample size during the inclusion process. The confidence in the original sample size was calculated using the primary outcome measure, so the primary endpoint was not missing and was not affected in any way. This study was a randomized double-blind trial, and all subjects were not blinded in the study, so the randomness of the scheme was not affected.

Reference:

1. Tang Y, Xing Y, Zhu Z, et al. The effects of 7-week cognitive training in patients with vascular cognitive impairment, no dementia (the Cog-VACCINE study): A randomized controlled trial. *Alzheimers Dement*. 2019;15(5):605-614. doi:10.1016/j.jalz.2019.01.009

2. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613. doi:10.1046/j.1525-1497.2001.016009606.x

3. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092-1097. doi:10.1001/archinte.166.10.1092