

Statistical Analysis Plan

Dense cranial electroacupuncture stimulation plus body acupuncture for adolescents with psychological distress: a randomized controlled trial with observations on salivary oxytocin and cortisol changes

Affiliated institution:

School of Chinese Medicine, LKS Faculty of Medicine, The University of Hong Kong

Principal Investigator

Zhang-Jin Zhang, MD, PhD

School of Chinese Medicine, LKS Faculty of Medicine, The University of Hong Kong

Tel no.: (+852)3917-6445

E-mail: zhangzj@hku.hk

Abbreviations

Abbreviations: BAI-C, Chinese version of the Beck Anxiety Inventory; C-BDI-II, Chinese version of Beck Depression Inventory II; DCEAS+BA, dense cranial electroacupuncture stimulation plus body acupuncture; MAS, minimal acupuncture stimulation; PSQI, Pittsburgh Sleep Quality Index; SAS, Zung Self-Rating Anxiety Scale; SDS, Zung Self-Rating Depression Scale; WHOQOL-BREF, World Health Organization Quality of Life-Brief.

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Introduction

This statistical analysis plan (SAP) describes the planned analyses to be performed on data collected in the clinical trial titled “Dense cranial electroacupuncture stimulation plus body acupuncture for adolescents with psychological distress: a randomized controlled trial with observations on salivary oxytocin and cortisol changes”. No statistical analyses will be performed until the final version of this SAP has been approved.

Study design

It is an assessor-blinded, randomized, MAS-controlled trial. A total of 148 eligible subjects will be recruited. They will be randomly assigned to either a “dense cranial electroacupuncture stimulation plus body acupuncture (DCEAS+BA)” group or a “minimal acupuncture stimulation (MAS)” control group, with 74 subjects per group for 8 weeks, followed by a 4-week post-treatment observation period.

Hypothesis and aims

The hypotheses of this trial are:

- (a) DCEAS+BA could alleviate anxiety, depression, and other related symptoms of adolescents; and
- (b) the therapeutic effects of DCEAS+BA may be associated with its enhancement of oxytocin and suppression of stress reactions.

The aims of this study are:

- (a) to compare the efficacy of DCEAS+BA and minimal acupuncture stimulation as a control in alleviating anxiety and depressive symptoms, and improving sleep quality;
- (b) to detect the effects of DCEAS+BA on salivary levels of oxytocin and cortisol and correlation with clinical improvement.

Patient population

Adolescents aged 15-22 years experiencing mild to moderate anxiety or depressive symptoms are eligible for enrolment.

Inclusion criteria

Subjects will be eligible for this study if they:

- (a) are aged 15-22 years;
- (b) are experiencing anxiety as evidenced by a BAI-C score of at least 8 (no symptoms = 0-7; mild = 8-15; moderate = 16-25; severe = 26-63), and/or a C-BDI-II score of at least 14 (no symptoms = 0-13, mild = 14-19; moderate = 20-28; severe = 29-63); ^{1,2}
- (c) have symptoms that have persisted for more than 3 months;

- (d) are able to provide informed consent for participation, and complete treatments and questionnaires as scheduled; and
- (e) have no suicidal ideation, as evidenced by “no” answers or a score of <3 for all questionnaires of the Columbia-Suicide Severity Rating Scale (C-SSRS).

Exclusion criteria

Subjects will be excluded if they:

- (a) have unstable systemic medical conditions that may limit their participation in the study, for example, severe liver, cardiovascular, or kidney impairment; gastrointestinal or endocrine dysfunction; malignancy; autoimmune disease; acute infectious disease; or any conditions with unstable vital signs or require intensive hospitalization;
- (b) have bipolar or psychotic disorder (e.g. schizophrenia);
- (c) have a history of brain injury or surgery;
- (d) have alcohol abuse or substance abuse;
- (e) are pregnant or in lactation, or intend to conceive;
- (f) have heart pacemaker or other metal devices implanted in the body;
- (g) have concurrent or use of drug treatment for anxiety/depression in the previous 6 months;
- (h) have treatment with acupuncture or brain stimulation in the previous 6 months;
- (i) have a history of epilepsy;
- (j) have a condition of bleeding tendency, or coagulopathy, or currently receiving anti-coagulant treatment; or
- (k) involved in other interventional clinical studies in the last 3 months or any relevant condition potentially interfering with study evaluation.

Randomization, central allocation and blindness

One independent research assistant will be in charge of randomization and central allocation. After confirmation of patients' eligibility and completion of the baseline assessment, participants will be randomly assigned to DCEAS+BA or MAS groups in a ratio of 1:1. Random codes were produced in advance using simple, complete, non-sequential numbers, with a block of 2, 4 or 6, through a random allocation software at <http://mahmoodsaghaei.tripod.com/Softwares/randalloc.html>. Randomization information will be sealed in sequentially numbered opaque envelopes.

Central allocation will be conducted, i.e., site investigators who are responsible for subjects' eligibility will obtain the opaque envelope from the central coordinator for an eligible subject who will be allocated to one of the two groups. Each envelope will be opened by acupuncturists after the participant completes the baseline assessment. Clinical assessors and data analysts will be blind to patients' treatment.

Intervention

- (a) DCEAS plus body acupuncture regimen: Subjects assigned to the DCEAS+BA group will receive DCEAS+BA treatment, 2 sessions per week for 8 consecutive weeks. Details of selected acupoints and treatment procedures can be found in the study protocol.

(b) MAS regimen: Subjects assigned to the MAS group will receive MAS treatment, 2 sessions per week for 8 consecutive weeks. Details of selected acupoints and treatment procedures can be found in the study protocol.

Study outcomes

Primary outcome

The primary outcome will be evaluated by the mean change of the Chinese version of the Beck Anxiety Inventory (BAI-C) score between baseline and endpoint. The BAI-C is a self-report inventory and a Likert scale that measures the scale quality of magnitude of anxiety.¹ Assessments will be conducted at baseline, week 4, week 8, and week 12 (post-intervention assessment).

Secondary outcomes

Assessments will be conducted at baseline, week 4, week 8, and week 12 (post-intervention assessment).

The secondary outcomes will include:

- (a) the Chinese version of Beck Depression Inventory II (C-BDI-II) for depressive symptoms;²
- (b) the Zung Self-Rating Anxiety Scale (SAS) for anxiety symptoms;³
- (c) the Zung Self-Rating Depression Scale (SDS) for depressive symptoms;⁴
- (d) the Pittsburgh Sleep Quality Index (PSQI) for sleep quality;⁵
- (e) the World Health Organization Quality of Life-Brief (WHOQOL-BREF) (HK version) for the general quality of life;⁶
- (f) salivary oxytocin level; and
- (g) salivary cortisol level.

Safety outcomes

The severity of adverse events (AEs) will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria.⁷ AEs will be systematically recorded, in which AEs that first appear in the study or worsen relative to the pre-study status will be recorded at each visit, including date and time of onset, duration, severity, relationship to intervention, and action taken accordingly. The causality between treatment procedures and AEs will be assessed.

Sample size determination

The improvement in anxiety symptoms will serve as the primary outcome (see below). We hence referred to controlled trials of acupuncture treatment of anxiety disorders for the sample estimation. However, most of these trials used anxiolytics and antidepressants as controls.^{8,9} We therefore additionally referred to our two previous trials that evaluated the efficacy of DCEAS on major depressive disorder and DCEAS+BA on post-stroke depression

with sham acupuncture and MAS as control.^{10,11} The estimation is based on the following formula,

$$n = \frac{2}{(M/SD)^2} \times C_{p,power}$$

where n is the number of subjects required in each arm; M is the mean difference between the two groups. SD is the standard deviation. $C_{p,power}$ is equal to 7.9 when the two-tailed level of α and power ($1-\beta$) are set at 0.05 and 80%, respectively. The sample size estimation was based on 3 representative trials of acupuncture for anxiety disorders,¹²⁻¹⁴ and our two trials for depression.^{10,11} At a highly conservative level, it is expected that DCEAS could produce a significantly greater improvement than controls in reducing the severity of anxiety and depression, with a standard deviation (SD) equal to approximately 200% of the mean difference (M). It then requires 74 subjects per arm with an assumed dropout rate of 15%. We propose to recruit a total of 148 subjects ($n = 74$ for each group).

Data processing and analysis

General principles

One biostatistician who is blinded to interventions will be responsible for statistical analysis. The analysis will be carried out on the intention-to-treat (ITT) population. For all primary and secondary outcomes, two-tailed P-values will be reported in addition to confidence intervals. The nominal level of statistical significance (α) will be 5%. The analysis and reporting of the results will follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Analysis software

All analyses will be performed using R Studio version 4.0.0 or later.

Analysis Populations

All analyses will be carried out on the intention-to-treat (ITT) population, for which participants have been randomized, completed the baseline assessment regardless of protocol compliance.¹⁵ The flow of patients throughout the trial will be shown using a CONSORT diagram (Figure 1).

Demographic characteristics and baseline comparisons

Baseline comparisons will be tabulated for the following variables (Proposed Table 1):

- (a) Age, years
- (b) Gender (Categories: male / female)
- (c) Marital status (Categories: married or living with partner / single, separated, divorced, or widowed)
- (d) Education level (Categories: primary or below / lower secondary / upper secondary / university or above)
- (e) Occupation (Categories: student / full-time employee / part-time employee / unemployed / housework / others)
- (f) Diagnosis of mood disorders before (Categories: Yes / No)

- (g) Duration of present psychological distress, months
- (h) Number of relapse
- (i) Current medication of hypnotics (Categories: Yes / No)
- (j) Baseline BAI-C score
- (k) Baseline C-BDI-II score
- (l) Baseline SAS score
- (m) Baseline SDS score
- (n) Baseline PSQI score
- (o) Baseline WHOQOL-BREF and its subscales (physical health; psychological; social relationships; environment) scores
- (p) Baseline salivary oxytocin, pg/mL
- (q) Baseline salivary cortisol, nmol/L

Continuous variables will be presented using mean with standard deviation (SD). Student t-test will be used to detect differences in continuous baseline variables.

Categorical variables will be presented by counts with percentages. Percentages will be calculated according to the number of patients for whom data are available. Categorical variables will be analyzed using the Chi-square test or Fisher's exact test.

Discontinuation will be summarized by counts with percentages. Chi-square test or Fisher's exact test will be used to detect differences between the four groups.

Primary outcome

A linear mixed-effect model will be applied to compare the primary outcome (changes in total BAI-C score from baseline), with time (baseline, week 4, week 8 and week 12) and group (DCEAS+BA and MAS) as categorical fixed factors and random intercepts within a scaled identity covariance matrix. Gender, age, and baseline BAI-C score will serve as covariates. Two-tailed P-values will be reported in addition to confidence intervals ([Proposed Tables 2](#)).

Subgroup analysis will be further conducted to compare outcomes to detect whether these subgroup factors are associated with outcomes. The following subgroups include:

- (a) Age (15-18 years and 18-22 years);
- (b) Gender (male and female);
- (c) Baseline BAI-C score (mild [score: 8-15], moderate [score: 16-25], severe [score: 26-63]); and
- (d) Baseline C-BDI-II score of at least 14 (mild [score: 14-19], moderate [score: 20-28], severe [score: 29-63]).

Secondary outcomes

A linear mixed-effect model will be applied to compare the secondary outcomes, including changes in scores of the C-BDI-II, SAS, SDS, PSQI and WHOQOL-BREF, with time (baseline, week 4, week 8 and week 12) and group (DCEAS+BA and MAS) as categorical fixed factors and random intercepts within a scaled identity covariance matrix. Gender, age, and baseline BAI-C score will serve as covariates.

A linear mixed-effect model will be applied to compare changes in salivary oxytocin and cortisol levels, with time (baseline and week 8) and group (DCEAS+BA and MAS) as categorical fixed factors and random intercepts within a scaled identity covariance matrix. Gender, age, and baseline BAI-C score will serve as covariates. Linear regression will be conducted to examine inter-correlations between changes in clinical outcomes and biomarker levels.

Two-tailed P-values will be reported in addition to confidence intervals ([Proposed Tables 2](#)).

Safety outcomes

AEs related to treatment will be tabulated by treatment group without statistical tests or confidence intervals ([Proposed Table 3](#)).

All AEs that occurred throughout the trial will be tabulated by treatment group and AE category (mild, moderate, severe, life-threatening, or death). Chi-square test or Fisher's exact test will be used to detect differences between the four groups ([Proposed Table 4](#)).

Details of serious AEs and death cases will be summarized and listed in a separate table.

Interim analysis

No interim outcome analyses were done prior to the completion of the study to avoid assessment bias.

Missing data

A linear mixed-effect model will be conducted for all analyses of primary and secondary outcomes without imputation of missing data.¹⁶

Proposed Tables

Table 1. Baseline characteristics

Characteristic	DCEAS+BA (n=74)	MAS (n=74)	Total (n=148)	<i>P</i> value
Age, years ^a	XX ± XX	XX ± XX	XX ± XX	XX
Gender (Female) ^b	XX (XX)	XX (XX)	XX (XX)	XX
Marital status ^b				XX
Married or living with partner	XX (XX)	XX (XX)	XX (XX)	
Single, separated, divorced, or widowed	XX (XX)	XX (XX)	XX (XX)	
Education level ^b				XX
Primary or below	XX (XX)	XX (XX)	XX (XX)	
Lower Secondary	XX (XX)	XX (XX)	XX (XX)	
Upper Secondary	XX (XX)	XX (XX)	XX (XX)	
University or above	XX (XX)	XX (XX)	XX (XX)	
Past occupation ^b				XX
Student	XX (XX)	XX (XX)	XX (XX)	
Full-time employee	XX (XX)	XX (XX)	XX (XX)	
Part-time employee				
Unemployed	XX (XX)	XX (XX)	XX (XX)	
Housework	XX (XX)	XX (XX)	XX (XX)	
Others / no information	XX (XX)	XX (XX)	XX (XX)	
Have previous diagnosis of mood disorders ^b	XX (XX)	XX (XX)	XX (XX)	XX
Duration of present psychological distress, months ^a	XX ± XX	XX ± XX	XX ± XX	XX
Number of relapse ^a	XX ± XX	XX ± XX	XX ± XX	XX
Have current medication on hypnotics ^b	XX (XX)	XX (XX)	XX (XX)	
BAI-C ^a	XX ± XX	XX ± XX	XX ± XX	XX
C-BDI-II ^a	XX ± XX	XX ± XX	XX ± XX	XX
SAS ^a	XX ± XX	XX ± XX	XX ± XX	XX
SDS ^a	XX ± XX	XX ± XX	XX ± XX	XX
PSQI ^a	XX ± XX	XX ± XX	XX ± XX	XX
WHOQOL-BREF ^a	XX ± XX	XX ± XX	XX ± XX	XX
Physical health	XX ± XX	XX ± XX	XX ± XX	XX
Psychological	XX ± XX	XX ± XX	XX ± XX	XX
Social relationship	XX ± XX	XX ± XX	XX ± XX	XX
Environment	XX ± XX	XX ± XX	XX ± XX	XX
Salivary oxytocin, pg/mL ^a	XX ± XX	XX ± XX	XX ± XX	XX
Salivary cortisol, nmol/L ^a	XX ± XX	XX ± XX	XX ± XX	XX

Abbreviations: BAI-C, Chinese version of the Beck Anxiety Inventory; C-BDI-II, Chinese version of Beck Depression Inventory II; DCEAS+BA, dense cranial electroacupuncture stimulation plus body acupuncture; MAS, minimal acupuncture stimulation; PSQI, Pittsburgh Sleep Quality Index; SAS, Zung Self-Rating Anxiety Scale; SDS, Zung Self-Rating Depression Scale; WHOQOL-BREF, World Health Organization Quality of Life-Brief.

^a Continuous data are expressed as mean $\pm$ SD and were examined using Student t-test. Those which statistical differences $P < 0.05$ reached the significance level are indicated in bold font.

^b Categorical data are expressed as count (percentage) and were examined using Chi-square (χ^2) or Fisher Exact test. Those which statistical differences $P < 0.05$ reached the significance level are indicated in bold font.

Table 2. Primary and secondary outcomes

Outcomes	Change from baseline				Analysis (Between group)	
	DCEAS+BA (n=74)		MAS (n=74)			
	Mean (95%CI)	Within-group <i>P</i> value ^c	Mean (95%CI)	Within-group <i>P</i> value ^c	Difference Mean (95%CI)	<i>P</i> value ^d
Primary outcome						
BAI-C ^a						
Week-4	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-8	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Secondary outcomes						
C-BDI-II ^a						
Week-4	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-8	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
SAS ^a						
Week-4	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-8	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
SDS ^a						
Week-4	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-8	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
PSQI ^a						
Week-4	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-8	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
WHOQOL-BREF ^b						
Week-4	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-8	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
WHOQOL-BREF, physical health ^b						
Week-4	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-8	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
WHOQOL-BREF, psychological ^b						
Week-4	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-8	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
WHOQOL-BREF, social relationship ^b						
Week-4	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-8	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
WHOQOL-BREF, environment ^b						
Week-4	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-8	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Salivary oxytocin, pg/mL ^a						
Week-8	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Salivary cortisol, pg/mL ^b						
Week-8	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX

Abbreviations: BAI-C, Chinese version of the Beck Anxiety Inventory; C-BDI-II, Chinese version of Beck Depression Inventory II; DCEAS+BA, dense cranial electroacupuncture stimulation plus body acupuncture; MAS, minimal acupuncture stimulation; PSQI, Pittsburgh Sleep Quality Index; SAS, Zung Self-Rating Anxiety Scale; SDS, Zung Self-Rating Depression Scale; WHOQOL-BREF, World Health Organization Quality of Life-Brief.

^a A greater negative value represents improvement in symptoms.

^b A greater positive value represents improvement in symptoms.

^c Data was represented as change in the scores from baseline. *P* value was calculated using a mixed-effects model with baseline adjustment to illustrate pre- and post-treatment within-group differences. Those which statistical differences $P < 0.05$ reached significance level are indicated in bold font.

^d *P* value was calculated using a mixed-effects model with baseline adjustment to illustrate between-group differences. Those which statistical differences $P < 0.05$ reached significance level are indicated in bold font.

Table 3. Adverse events related to treatment, n (%) ^a

Adverse event	DCEAS+BA (n=74)	MAS (n=74)
Bleeding at the site of needling	XX (XX)	XX (XX)
Hematoma around the site of needling	XX (XX)	XX (XX)
Dizziness after treatment	XX (XX)	XX (XX)
Headache after treatment	XX (XX)	XX (XX)
Localized pain	XX (XX)	XX (XX)
Needle phobia	XX (XX)	XX (XX)

Abbreviations: DCEAS+BA, dense cranial electroacupuncture stimulation plus body acupuncture; MAS, minimal acupuncture stimulation.

^a Data was expressed as number of patients (%).

Table 4. Reported adverse events in different categories, n (%) ^a

Adverse Event Category	DCEAS+BA (n=74)	MAS (n=74)	P-value ^a
Any	XX (XX)	XX (XX)	XX
Mild	XX (XX)	XX (XX)	XX
Moderate	XX (XX)	XX (XX)	XX
Severe	XX (XX)	XX (XX)	XX
Life-threatening	XX (XX)	XX (XX)	XX
Death	XX (XX)	XX (XX)	XX

Abbreviations: DCEAS+BA, dense cranial electroacupuncture stimulation plus body acupuncture; MAS, minimal acupuncture stimulation.

^a Data was expressed as number of patients (%). Those which statistical differences $p < 0.05$ reached significance level are indicated in bold font.

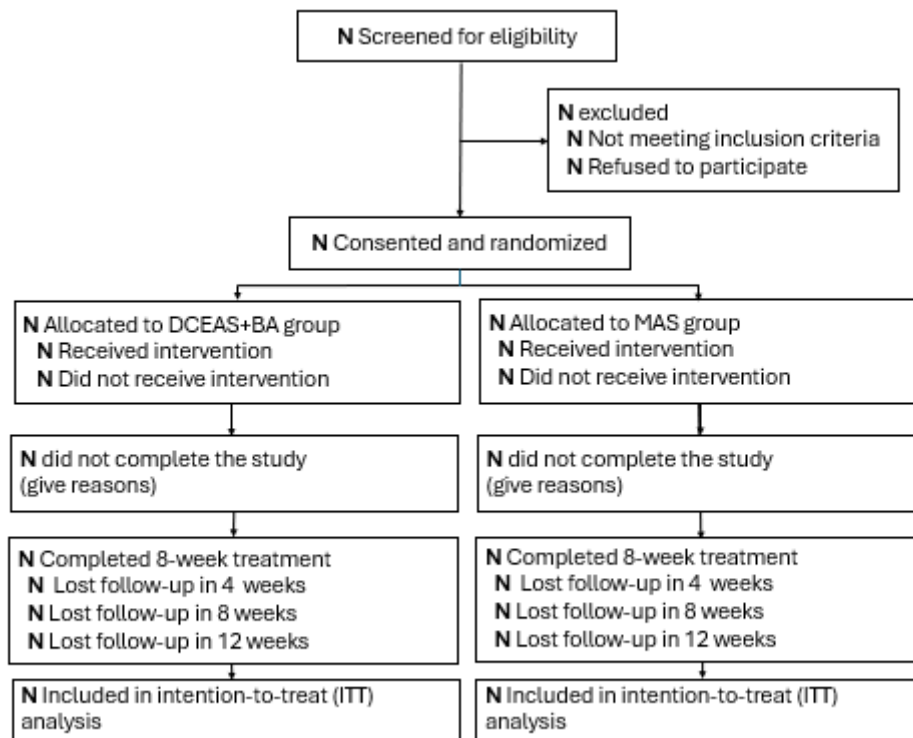


Figure 1. CONSORT Flowchart

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