Short title:	BRAINTRAIN SAP Template

Statistical Analysis Plan for

BRAINTRAIN: BCI (Brain Computer Interface) Intervention in Autism (BCIAUT)

Eudract/ISRCTN No:	[*NCT02445625*]	Version Number:	V 1.0

[Draft/Final/Amended] Plan

Based on protocol version [V 1.1 *and 14.02.2017*]:

SAP Revision History

Protocol version	Updated Sap version no.	Section number changed	Description and reason for change	Date changed

Short title:	BRAINTRAIN SAP Template

ROLES AND RESPONSIBILITIES

Trial Statistician: [*Bárbara Regadas Correia*]			
Role:			
Date:		Signature:	
Senior Statistician (or equivalent delegate): *[Bárbara Oliveiros]*			
Role:			
Date:		Signature:	
Chief Investigator (or Principle Investigator): *[Miguel Castelo-Branco]*			
Role:			
Date:		Signature:	
Other non-signatory contributor to the SAP: *[Name]*			
Role:			

TABLE OF CONTENTS

1. INTRODUCTION

This statistical analysis plan provides guidelines for the final presentation and analysis for the BCIAUT trial. This plan, along with all other documents relating to the analysis of this trial, will be stored in the Statistical Analysis Master File electronically and/or in hard signed copy formats.

2. BACKGROUND

2.1 RATIONALE AND RESEARCH QUESTION

Autism spectrum disorder (ASD) is a severe, early-onset and life-long neurodevelopmental disorder with a high worldwide prevalence and a distribution of four males (M) to one female (F) (Baron-Cohen et al., 2009; Fombonne, 2003; Oliveira et al., 2007). ASD is characterized by deficits in social interaction and communication as well as by a repetitive pattern of behaviour and interests (American Psychiatric Association, 2013).

Clinical research studies proved that ASD children show a deficit in interpreting others intentions from gaze-direction (Baron-Cohen et al., 1997; Baron-Cohen, 1989). ASD subjects also demonstrated a lack of attentional modulation in a fMRI study especially evident for social stimuli (Bird, Catmur, Silani, Frith, & Frith, 2006).

Individuals with ASD often have relatively strong visual processing skills and a preference towards electronic media, thus it is likely that the dissemination of intervention via computer technology would be particularly appropriate and motivating for these individuals (Shane & Albert, 2008).

The intervention comprises seven BCI sessions spread over four months. In each session, the subject is asked to identify objects of interest based on the gaze direction of an avatar. The subject response is interpreted from the EEG signal (using the P300 component, as established in our previous work).

The purpose of the study is to investigate whether a brain computer interface (BCI) can be used to train social cognition skills (in particular interpretation of gaze direction pointing to objects of interest) in ASD patients and whether this improves clinical symptoms (improvements in identification of social cues and improvement of overall social behaviour).

2.2 OBJECTIVES

The main hypothesis is that training of initiation and response to joint attention cues using gaming/BCI interfaces can be used to improve joint attention social cognition skills in ASD participants.

The primary goal is to ensure increased rate of responses to joint attention cues and improvement of social attention skills.

The secondary objectives are improvements in general aspects of social cognition (as measured by neuropsychological tests) derived from a generalization of the skills learned.

3. STUDY MATERIALS

3.1 TRIAL DESIGN

A Prospective, Single Arm, Longitudinal Cohort Study to assess improvement social attention in ASD (a BCI approach).

The eligible patients for the study will be subject to the same experience during 4 months and will be evaluated before (session 1) and after intervention (session 7 and follow-up).

3.2 RANDOMISATION

Not applicable

3.3 SAMPLE SIZE

To determine de sample size, we used the G*Power tool (Faul, Erdfelder, Lang & Buchner, 2007):

Test family: t-test;
Statistical test: Means (difference between two different means);
Type of power analysis: A priori;
Fixed input parameters: Tail(s): Two;
α err prob: 0.05;
Output: Estimated sample size

		Effect Size dz (ES)			
		0.8	0.9	1.0	1.1
Power	0.7	12	10	9	8
	0.8	15	12	10	9
	0.9	19	16	13	11

with $ES = Cohen's\ dz = \frac{M_{diff}}{\sqrt{\frac{\Sigma\left(X_{diff}-M_{diff}\right)^2}{N-1}}}$. Based in other effects described in the literature, the effect size considered is 0.8 (the means difference is 0.8 standard deviations). In these conditions, for power of 0.8 the estimated sample size is 15.

Without the normality assumption of the distribution of the means differences, we would also need 15 subjects, considering a non-parametric test.

Assuming a 20% dropout rate (based on literature) the sample size will be 18.

3.4 FRAMEWORK

The trial protocol states the main objective is that training of initiation and response to joint attention cues using gaming/BCI interfaces can be used to improve joint attention social cognition skills in ASD participants. Therefore, the main outcomes are testing for superiority rather.

3.5 INTERIM ANALYSES

Not applicable.

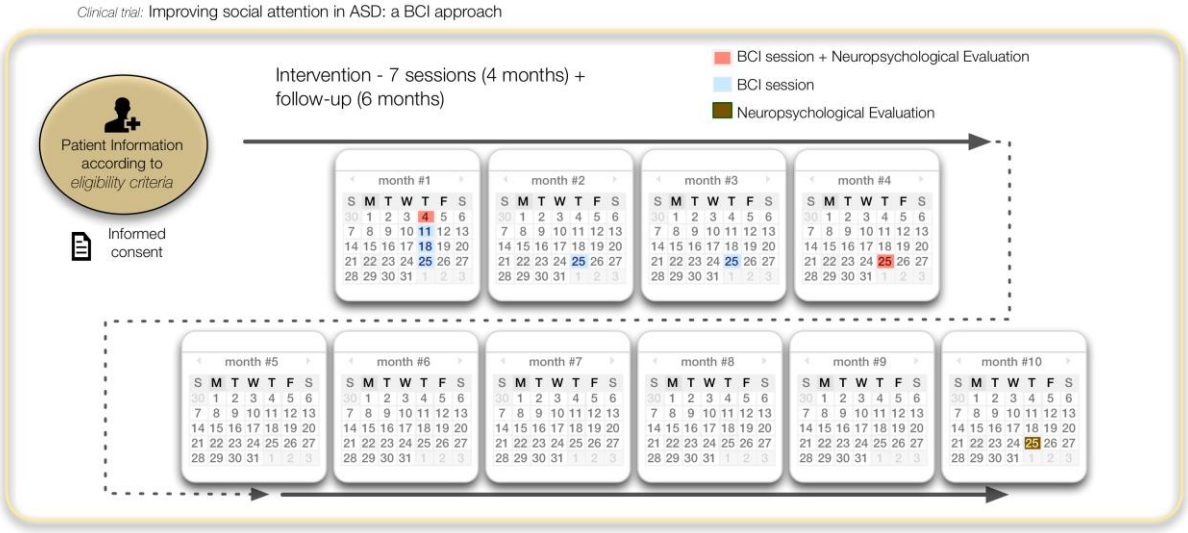
3.5.1 PLANNED SAMPLE SIZE ADJUSTMENT

3.5.2 STOPPING RULES

3.6 TIMING OF FINAL ANALYSIS

The intervention comprises seven BCI sessions spread over four months. In each session, the subject is asked to identify objects of interest based on the gaze direction of an avatar. Each subject will also undergo neuropsychological evolutions and "Joint-attention task" before the first session, after the last session (short-term) and in follow-up (long-term).

3.7 TIMING OF OUTCOME ASSESSMENT



4. STATISTICAL PRINCIPLES

4.1 LEVELS OF CONFIDENCE AND P-VALUES

All confidence intervals presented will be 95% and two-sided.

4.1.1 ADJUSTMENT FOR MULTIPLICITY

n/a

4.2 ADHERENCE AND PROTOCOL DEVIATIONS

4.2.1 DEFINITION AND ASSESSSMENT OF ADHERENCE

Adherence is defined as attending all seven BCI sessions.

Compliance is assessed based on the percent of subjects who have performed the scheduled number of interventional sessions. It is defined as:

% compliance = (number of sessions performed / number of planned sessions)*100%.

The number of planned sessions in this study is 7.

4.2.2 PRESENTATION OF ADHERENCE

Frequencies table and descriptive statistics of the adherence and "% compliance" will be summarized.

4.2.3 DEFINITION OF PROTOCOL DEVIATION

Physical incapacity to perform the tasks proposed.

4.2.4 PRESENTATION OF PROTOCOL DEVIATIONS

Register of number and type of protocol deviation and number of participants removed. No formal statistical testing will be undertaken.

4.3 ANALYSIS POPULATION

The intention-to-treat population will include all participants irrespective of number of session completed. If required the Centre for Trials Research will investigate methods of analysis that adjust for the number of sessions completed which is preferable to excluding participants which may result in biased results.

5. STUDY POPULATION

5.1 SCREENING DATA

Not applicable.

5.2 ELIGIBILITY

The number of participants eligible and how many were excluded due to violating each inclusion/exclusion criteria will be tabulated.

5.3 RECRUITMENT

A CONSORT flow diagram will be used to summarize the number of patients who were:

- assessed for eligibility
- lost to follow-up*
- discontinued the intervention*.

*reasons will be provided

5.4 WITHDRAWAL/FOLLOW UP

5.4.1 LEVEL OF WITHDRAWAL

The level of withdrawal will be tabulated, considering these aspects:

- Withdrawal from study intervention
- Withdrawal from study follow-up
- Withdrawal from entire study and does not want data to be used.

5.4.2 TIMING OF WITHDRAWAL

Timing of withdrawal from follow-up or lost to follow up data will be presented in a table. For each time point information on the number of withdrawals and reasons for withdrawal will be provided.

5.4.3 REASONS FOR WITHDRAWAL

A patient may withdraw or be withdrawn from the intervention for the following reasons:

- Withdrawal of consent for intervention by the participant
- Any alteration in the participants condition or circumstances which justifies the discontinuation of the intervention in the Investigators' opinion.

5.4.4 PRESENTATION OF WITHDRAWAL/LOSS TO FOLLOW-UP

The numbers (with reasons) of losses to follow-up (drop-outs and withdrawals) over the course of the study will be summarised in a table.

5.5 BASELINE PARTICPANT CHARACTERISTICS

5.5.1 LIST OF BASELINE DATA

Measure	Outcomes	Description
Demographic questionnaire	Age, gender, education, SES	
Thought control questionnaire (TCQ)(Wells & Davies, 1994)	Thought control (distraction, punishment, worry; re-appraisal; social control)	30-item measure to assess effectiveness of strategies used for the control of unpleasant/unwanted thoughts
Thought control ability questionnaire (TCAQ)(Luciano et al., 2005)	Thought control	25-item measure of individual differences in perceived ability to control unwanted & intrusive thoughts
Wechsler Adult Intelligence Scale (WAIS-III)(Wechsler, 1997)	IQ	Global intelligence/IQ measure

5.5.2 DESCRIPTIVE STATISTICS

Categorical data will be summarised by numbers and percentages. Continuous data will be summarised by mean, standard deviation, minimum and maximum values. Tests of statistical significance will not be undertaken for baseline characteristics.

6. ANALYSIS

6.1 PROGRESSION CRITERIA

Since this study represents a feasibility trial this is not applicable.

6.2 OUTCOME DEFINITIONS

Criteria	Level	Action
Consent rate	>50%	GO
	30-50%	Potential mitigating strategies
	<30%	STOP
Retention rate	>80%	GO
	50-80%	Potential mitigating strategies
	<50%	STOP
Intervention uptake: % of patients in the intervention group commencing the intervention	>90%	GO
	60-90%	Potential mitigating strategies
	<60%	STOP
Intervention adherence: % of attendance rates for patients in the intervention group	>80%	GO
	50%-80%	Potential mitigating strategies
	<50%	STOP
Acceptability of research processes and intervention assessed via qualitative interviews	Majority of reports positive	GO
	Minor issues identified that can potentially be resolved	Potential mitigating strategies
	Major problems with acceptability reported	STOP
Potential contamination assessed via qualitative interviews	Majority of reports positive	GO
	Minor issues identified that can potentially be resolved	Potential mitigating strategies
	Major problems with contamination reported	STOP

6.2.1 PRIMARY OUTCOME(S)

The results [Number of items of social attention that a patient can accurately identify in the avatar's action, e.g. looking at, pointing at] in a separate "Joint-attention task" will be the primary outcome measure. The experimental group will be evaluated in the pre (session 1) and post intervention (session 7 and follow-up).

6.2.2 TIMING, UNITS AND DERIVATION OF PRIMARY

The experimental group will be evaluated in the pre (session 1) and post intervention (session 7 and follow-up).

6.2.3 LIST OF SECONDARY OUTCOMES

The results in Autism Treatment Evaluation Checklist (ATEC) [Sociability and Cognitive Awareness Subtests] and the results in Vineland Adaptive Behavior Scale (VABS) [Socialization and Daily Living Skills Domains] will be the secondary outcome measures. The group will be evaluated in the pre (session 1) and post intervention (session 7 and follow-up).

6.2.4 ORDER OF TESTING

Not applicable

6.2.5 TIMING, UNITS AND DERVICATION OF SECONDARYS

The experimental group will be evaluated in the pre (session 1) and post intervention (session 7 and follow-up).

6.3 ANALYSIS METHODS

6.3.1 LIST OF METHODS AND PRESENTATION

Initially will conduct an exploratory data analysis using graphical techniques (box and scatter plots) and quantitative analysis (statistical measures and frequency table) in order to characterize the sample, detect possible extreme outliers and measurement error.
To detect differences between the three time points of neuropsychological evaluation (session 1, session 7 and follow-up) will perform the Repeated-measures ANOVA. To identify the difference between each evaluation, 95% confidence intervals will be presented. (Note: considering a normal distribution)

6.3.2 COVARIATE ADJUSTMENT

Not applicable.

6.3.3 ASSUMPTION CHECKING

The Shapiro Wilks test will be performed to evaluate the normality.

6.3.4 ALTERNATIVE METHODS IF DISTRIBUTIONAL ASSUMPTIONS NOT MET

Without the normality assumption, we will consider a non-parametric tests: Friedman test and Wilcoxon or Sign test. Since the primary outcome is a count variable it may be more suited to methods that utilize the Poisson distribution. If the primary outcome conforms to a Poisson distribution rather than a normal distribution then Poisson regression will be considered. Effect estimates and 95% confidence intervals will be tabulated.

6.3.5 SENSITIVITY ANALYSES

Not applicable.

6.3.6 SUBGROUP ANALYSES

Not applicable.

6.4 MISSING DATA

Mean imputation, this is, the replacement of a missing observation with the mean of the non-missing observations for that variable.

6.5 ADDITIONAL ANALYSES

Not applicable.

6.6 HARMS

The number (and percentage) of patients experiencing each AE/SAE will be presented categorised by severity. For each patient, only the maximum severity experienced of each type of AE will be displayed. The number (and percentage) of occurrences of each AE/SAE will also be presented. No formal statistical testing will be undertaken.

6.7 STATISTICAL SOFTWARE

The analysis will be carried out using SPSS 23.0.

7. REFERENCES

7.1 NON STANDARD STATISTICAL METHODS

Not applicable.

7.2 DATA MANAGEMENT PLAN

This documents follows the instructions stated in the Data Management Plan (DMP) version 1.0.

7.3 TRIAL MASTER FILE AND STATISTICAL MASTER FILE

7.4 OTHER SOPS OR GUIDANCE DOCUMENTS

SAP DEVIATION LOG

Document number:		**Document version:**	
Reason for deviation:			