STATISTICAL ANALYSIS PLAN (SAP) for ACTION-MS: A phase II randomised, assessor blinded, investigator-lead trial of a tailored cognitive behavioural therapy intervention versus supportive listening for depression in individuals newly diagnosed with multiple sclerosis

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Abbreviations

BDI-II	Beck Depression Inventory-II
DSMC	Data and Safety Monitoring Committee
ITT	Intention to Treat Analysis
STAI	State Trait Anxiety Inventory
CBT	Cognitive Behavioural Therapy
SL	Supportive Listening

1 STUDY DESIGN

1.1 OVERVIEW

The study is a prospective, parallel group, assessor-blind randomized controlled single centre (hospital sites in Victoria, Australia) trial among 60 adult participants who have been newly diagnosed with MS (within 5 years of having received a diagnosis) with mild to moderate depression (score between 14-28 on the BDI-II). Potential participants were screened for entry into the trial by neurologists, nurses and psychologists at RMH, St Vs, Austin Health and Western Health using a 1-page screening questionnaire. The primary site was the RMH city campus and the assessments and interventions were conducted at RMH city campus. Patients were randomized into either the tailored cognitive behavioral therapy (CBT) intervention or the supportive listening intervention. Randomisation with permuted blocks of different sizes into the tailored CBT intervention and supportive listening interventions (1:1 ratio) were undertaken via a secure, web-based Electronic Case Report Form (ECRF) System hosted by the Florey Institute of Neuroscience and Mental Health, Melbourne, Victoria, Australia. The randomization was stratified by depression severity (mild and moderate depression classified using the BDI-II). Randomisation occurred once participants were identified as scoring within the mild to moderate symptoms range on the BDI-II and confirmed by the pre-assessment clinical interview. Patients undertook a clinical interview, completed a set of questionnaires and were asked to provide blood and saliva samples at baseline, at post (immediately after taking part in the intervention they have been allocated) and at a 3 month follow up timepoint.

1.2 AIMS AND HYPOTHESES

The current trial will specifically address the following aims:

The primary aim of this study is to assess the efficacy of a tailored early CBT intervention, in treating depression (primary outcome) in individuals who have been newly diagnosed with MS and are experiencing mild to moderate depression.

Secondary aims of the study are to examine whether those that undertake the CBT intervention will also display significant and clinically meaningful reductions in levels of anxiety.

Tertiary aims of the study are to examine whether those that undertake the early tailored CBT intervention will also display significantly and clinically meaningful reductions in fatigue and pain impact, and significant improvements in sleep quality, MS related QOL, active coping styles, level of MS diagnosis acceptance, resilience and social support.

Quaternary aims of the study is to examine patient satisfaction and acceptability of the interventions and therapeutic alliance will also be examined.

Cost-effectiveness of interventions

Additionally, information will be collected to examine the cost-effectiveness of both interventions by assessing benefits to patients, effects on health service usage and other costs to society, and cost of providing the interventions. Levels of inflammatory cytokines across the three timepoints (baseline, post intervention and 3mth follow up) will also be collected.

Cytokine analyses

Levels of cytokines via saliva and blood collection across the three timepoints (baseline, post intervention and 3mth follow up) will also be collected. Once funding is secured this data will be analyze and published separately to the main effectiveness paper.

The reporting of the cost-effectiveness and cytokine analysis will be undertaken once funding is secured to analyze this data and will be published separately to the main effectiveness paper.

Primary hypothesis:

We hypothesize that there will be a significantly higher proportion of participants who achieve a clinically meaningful change of 10 points or more on the Beck Depression Inventory-2 (BDI-II) between baseline and post in the early CBT intervention compared to those receiving the Supportive Listening intervention.

Secondary hypotheses:

We hypothesize that those in the tailored early CBT intervention will display a significantly greater change in the BDI-II total score at 3 months follow up compared to those in the Supportive Listening intervention.

We hypothesize that those in the tailored CBT intervention will display a significant reduction on the State Trait Anxiety Inventory (STAI) at post compared to those receiving the SL intervention.

Tertiary hypotheses:

We hypothesize that those in the tailored early CBT intervention will display a significant reduction on the STAI total score at 3 months follow up compared to those in the Supportive Listening intervention.

We hypothesize that compared to those in the Supportive Listening intervention, participants in the tailored early CBT intervention will display significant reductions in fatigue and pain impact and significant improvements in level of MS illness acceptance, MS related quality of life, sleep quality, active coping strategies, resilience at post and 3-months follow up.

Exploratory hypotheses relating to cost-effectiveness and cytokine analyses:

There are no set hypotheses for the cost-effectiveness analyses although we expect that the tailored CBT intervention will prove cost-effective. We also expect that pro-inflammatory cytokines are reduced at post-intervention and 3 month follow up intervention as a result of undertaking the tailored CBT intervention.

1.3 PATIENT POPULATION

Inclusion criteria

Patients who are:

- 18 years and older,
- who are mild to moderately depressed (score mild to moderate on the BDI-II self report scale), and
- within 5 years of having received an MS diagnosis from a neurologist.

Exclusion criteria

Gross cognitive impairment that would make participation in the 8 one our sessions of CBT distressing;

- Unable to speak or read English;
- Acute organic brain syndrome (e.g., delirium);
- Serious psychological disorder (e.g., psychosis);
- Assessed with the BDI-II and he SCID-5 as being severely depressed;
- Already undertaking psychological treatment for depression/anxiety; or
- Taking antidepressants for less than two months.

1.4 SUMMARY OF PROTOCOL CHANGES

Due to COVID-19 related lockdowns in Melbourne, Victoria, Australia during 1st March, 2019 until December, 2022 there were disruptions and closures to health care services in Melbourne, Victoria, Australia. As a result of these lockdowns, all participants recruited into the trial from March, 2019 onwards were given the option of seeing trial psychologists via telehealth (video linkage) for their therapy session as part of the CBT and SL interventions and for their clinical interview assessments. The MS clinics located in the four major hospitals in Melbourne, Victoria, Australia offered services via telehealth (video linkage) during and beyond the COVID-19 lockdowns. Modality of therapy sessions was subsequently included as a covariate as part of all analyses.

1.5 RANDOMIZATION

Randomisation with permuted blocks of different sizes into the tailored CBT intervention and supportive listening arms (1:1 ratio) was undertaken via a secure, web-based Electronic Case Report Form (ECRF) System hosted by the Florey Institute of Neuroscience and Mental Health, University of Melbourne, Victoria, Australia. The randomization was stratified by depression severity (mild and moderate depression classified using the BDI-II). Randomisation will occur once participants are identified as scoring within the mild to moderate symptoms range on the BDI-II. All online submissions are secured by use of password site entry and data encryption procedures. Once patient recruitment data are submitted online by the assessing psychologists, the randomization allocation is immediately provided to the investigator or trial manager.

1.6 BASELINE, POST AND FOLLOW-UP ASSESSMENTS

All potential participants will undertake a pre-assessment clinical interview with a psychologist at RMH. During the pre, post and 3-month assessment clinical interviews all potential participants will be screened for the presence of a Major Depressive Disorder using the clinical trials version of the Structured Clinical Interview for DSM-5 (SCID-5). The assessing psychologist will score the results of the self-report and interview data. If the potential participant scores within the mild to moderate symptom range on the BDI-II, they will be offered the 8-week intervention. The assessing psychologist will inform the Clinical Trials Manager who will contact participants regarding their treatment allocation (i.e., either CBT or SL intervention) and organise the first therapy session with another psychologist employed in the current research trial. The psychologists undertaking assessments will be separate from the psychologists offering the interventions. Therefore researchers on this trial and psychologists conducting the assessment will not know a patient's treatment allocation, while treating psychologists and trial manager will be unblinded to the intervention type.

At pre- and post-treatment and 3 month follow up, participants will also be asked to provide blood and saliva samples to examine levels of inflammatory cytokines. A platform of cytokines known to be associated with depression (e.g., interleukin 6 and 9, tumor necrosis factor-alpha) will be assessed. Professor O'Brien-Simpson will advise on all immunological/platelet/HPA assays, and will supervise the research assistant carrying out all assays in his laboratory and will assist in the interpretation of immunology results and manuscript preparation. Participants will also be asked to complete questionnaires at pre-intervention, post-intervention, and at 3- month follow up. These will be completed online and information will be stored on REDCap. Participants will also have the option of completing the questionnaires in paper format if they prefer.

1.7 SAMPLE SIZE

Based on MS clinic data gathered from RMH, at least 90 newly diagnosed MS patients who are seen at the MS clinics in three hospital campuses (Royal Melbourne Hospital, St Vincent's Hospital, Western Health)) will be approached in order to obtain a total sample size of 60 (30 in each group). This is based on a recruitment rate of 67% from our Phase I pilot trial of this intervention (Kiropoulos et al., 2020).

1.8 UNBLINDING

There is no scheduled interim data analysis. Treatment allocations are securely stored and separated from investigators. Statisticians not involved in the Data and Statistical Management Board (DSMB) will remain blinded and work on dummy datasets until the computer scripts for statistical analyses are validated. The DSMB Chair is Associate Professor Isabel Krug, University of Melbourne, Victoria, Australia.

1.9 COMPLETION OF INTERVENTIONS

Four out of the 8 sessions need to be completed for participants to be classified as 'completed' either the CBT or SL intervention.

1.10 OUTCOMES

1.10.1 Primary Outcome

For this clinical trial, outcome measures include self-report questionnaires.

Percentage of participants achieving a clinically meaningful change of 10 points or more on the BDI-II between baseline and post in the tailored CBT intervention. Level of depression will be measured with the BDI-II which has been found to have excellent psychometric properties and previously used in MS populations.

1.10.2 Secondary Outcomes

Magnitude of change between baseline and 3-months follow up on the BDI-II in the tailored CBT intervention. Level of depression will be measured with the BDI-II. Magnitude of change between

baseline and post-assessment and 3 month follow up on the STAI. Level of anxiety will be measured with the STAI.

1.10.3 Tertiary Outcomes

Magnitude of change between baseline and post-assessment on fatigue and pain impact, MS related quality of life, sleep quality, MS diagnosis acceptance, active coping styles, resilience, and perceived social support in the early CBT intervention. Fatigue impact will be measured with the Modified Fatigue Impact Scale-5 item version (MFIS-5) taken from the Multiple Sclerosis Quality of Life Inventory. Pain impact will be measured using the 6-item Pain Effects Scale. Sleep quality was examined using the Pittsburgh Sleep Quality. MS related quality of life was measured using the 54-item MS-related quality of life measure. Coping styles will be examined using the 66-item Ways of Coping questionnaire. Acceptance of MS illness will be measured using the 10-item Acceptance of Chronic Health Conditions Scale. Level of resilience will be measured with the 33-item Resilience Scale for Adults used to investigate five main protective factors: personal competence, social competence, personal structure, family cohesion and social resources. Perceived social support will be measured using the 12-item Perceived Social Support Scale.

1.10.4 Quartenary Outcomes

Cost-effectiveness will be explored in terms of quality-adjusted life years using the EuroQoL-5D measure of health-related quality of life which is a validated measure used in previous psychological intervention trials for depression. Self-report questions at baseline, post, 3-month follow up will also assess participant's direct treatment costs including contacts with primary and secondary public health services, use of psychotropic drugs, and private health services. Indirect non-treatment costs will also be collected which will include child care and travel, travel costs to secondary care, employment status, weeks worked, current wage rate, and an estimate of time lost from work through illness. Patient acceptability and satisfaction will be measured with the tailored CBT and SL interventions at post-assessment using the Acceptability and Satisfaction questionnaire developed by the Principle Investigator for this purpose. Therapeutic alliance will also be measured with the Working Alliance Questionnaire and Helping Alliance Questionnaire.

1.10.5 Serious Adverse Events

Serious Adverse Events (SAEs) were considered to be a suicide attempt or hospitalisation for a suicide attempt. Assessment of suicidal ideation, suicide intent, plans and actions will be monitored by therapists in every session and they will use the BDI-II item on suicidal ideation, intent, plan and action to monitor their client. It should be noted that we have screened out severely depressed individuals (those scoring >28 on the BDI-II) and all individuals participating in the trial have scored in the mild-moderate (14-28) on the BDI-II. All SAE's will be documented by the Principal Investigator.

2 FUNDING

This work was supported by a Multiple Sclerosis Research Australia Project Grant (Grant Number 15-013). This funding source has no influence on the design of the study and has not influenced its execution, analyses, interpretation of the data or decision to submit results.

STATISTICAL ANALYSIS

2.1 ANALYSIS PRINCIPLES AND GENERAL CONSIDERATIONS

Primary: Hypothesis 1: The primary outcome analysis will be an intention to treat between-group comparison of the proportion of patients who achieve a clinical and meaningful change of 10 points or more on the BDI-II between baseline and post adjusted for baseline depression severity using a logistic regression model. We will assess heterogeneity of effect due to multiple sites with a mixed-effect multi-level regression model treating site as a random effect.
Secondary and Tertiary Hypotheses: These outcomes will be analysed using appropriate regression models adjusted as above. Longitudinal changes will be examined using correspondence mixed effect regression models. No formal interim analyses for either efficacy or safety are planned, but safety outcomes will be continuously monitored by an independent DSMB.

2.2 POWER CALCULATIONS

The current study is powered for the primary outcome of the proportion of patients who achieve a clinically meaningful change of 10 points or more on the BDI-II between baseline and post in the early CBT intervention compared to those receiving the supportive listening intervention. Based on pilot study data (the proportion of those obtaining a good outcome in the CBT group (0.6) and the TAU group (0)), it is envisaged that recruiting 30 patients per group is feasible within the proposed 3-year time frame. This number will yield 90% power using an $\alpha = 0.05$ threshold to observe a conservatively estimated 45% difference in the proportion of patients achieving a favourable primary outcome. The proposed sample size has also been inflated for potential drop-outs at post and 3 months.

2.3 INTERIM ANALYSES

No interim analyses are planned.

2.4 TRIAL PROFILE

Flow of patients through the study will be displayed in a standard CONSORT diagram. The flowchart will included the number of patients recruited, included in the trial, those who withdrew and were lost to follow up, the number who received the allocated treatment and were analysed (Figure 1 – Standard CONSORT Flowchart).

2.5 PATIENT CHARACTERISTICS AND BASELINE COMPARISONS

Description of the specified baseline characteristics will be presented for the two treatment arms. Discrete variables will be summarized as frequencies and percentages. Unless otherwise indicated in the tables, percentages will be calculated according to the number of patients for whom data are available. Continuous variables will be summarized by use of either mean and standard deviation (SD) or median or interquartile range (IQR).

2.6 PRIMARY OUTCOME

2.6.1 Outcome measure

Primary: Hypothesis 1: The proportion of patients who achieve a clinical and meaningful change of 10 points or more on the BDI-II between baseline and post adjusted for baseline depression severity using a logistic

regression model. We will assess heterogeneity of effect due to multiple sites with a mixed-effect multi-level regression model treating site as a random effect.

2.6.2 Statistical Hypotheses

The null hypothesis will be rejected if the proportion of patients in the tailored CBT intervention will achieve a change of 10 points or more on the BDI-II from baseline to post assessment compared to the supportive listening intervention.

2.6.3 Treatment of missing values

It is anticipated that there will be minimal missing primary outcome data. All randomized subjects are to be included in the primary ITT outcome analysis.

2.6.4 Analysis method

The proportion of patients who achieve a change of 10 or more points on level of depression as measured with the BDI-II will be compared between the tailored CBT intervention and the Supportive Listening intervention using a binary logistic regression, adjusted for the baseline level of depression. The treatment effect will be presented as an odds ratio (OR) with the corresponding 95% CI.

2.7 SECONDARY OUTCOME:

2.7.1 Outcome measure

Secondary Hypothesis 2 & 3: Magnitude of change between baseline and 3 months on the level of depression as measured with the BDI-II will be compared between the tailored CBT intervention and the Supportive Listening intervention. Magnitude of change between baseline and post on level of anxiety as measured with the STAI will be compared between the tailored CBT intervention and the Supportive Listening intervention.

2.7.2 Statistical Hypotheses

Individuals in the tailored CBT intervention will have lower level of depression and level of anxiety from baseline to 3 months compared to those in the Supportive Listening intervention.

2.7.3 Treatment of missing values

It is anticipated that there will be minimal missing primary outcome data. All randomized subjects are to be included in the primary ITT outcome analysis.

2.7.4 Analysis method

These outcomes will be analysed using appropriate regression models adjusted for the baseline level of depression. Longitudinal changes will be examined using correspondence mixed effect regression models. The treatment effect will be presented as an odds ratio (OR) with the corresponding 95% CI.

2.8 TERTIARY OUTCOMES:

2.8.1 Outcome measures

Magnitude of change between baseline and post treatment on fatigue interference and pain impact, MS related quality of life, sleep quality, MS diagnosis acceptance, active coping styles, resilience and perceived

social support will be compared between the tailored CBT intervention and the Supportive Listening intervention.

2.8.2 Statistical Hypotheses

Individuals in the tailored CBT intervention will report lower levels of fatigue interference, pain impact compared to those in the Supportive Listening intervention. Individuals in the tailored CBT intervention will have higher levels of MS related quality of life, sleep quality, MS diagnosis acceptance, resilience, active coping styles and perceived social support.

2.8.3 Treatment of missing values

It is anticipated that there will be minimal missing primary outcome data. All randomized subjects are to be included in the primary ITT outcome analysis.

2.8.4 Analysis method

These outcomes will be analysed using appropriate regression models adjusted for the baseline level of depression. Longitudinal changes will be examined using correspondence mixed effect regression models. The treatment effect will be presented as an odds ratio (OR) with the corresponding 95% CI.

2.9 QUARTENARY OUTCOMES:

2.9.1 Outcome measures

Participants will be asked to record service use including all types and duration of hospital admissions, frequency of outpatient hospital appointments, MS-related community service use, anti-depressant and anti-anxiety medication use and cost and paid and unpaid work using the Client Service Receipt Inventory [39]. Health-related quality of life data and quality-adjusted life years (QALYs) will be assessed using the health-related quality of life measure (EuroQoL-5D). The difference in these estimates between the tailored CBT and Supportive Listening interventions will be examined.

Patient acceptability and satisfaction will be measured with the tailored CBT and SL interventions at post-assessment using the Acceptability and Satisfaction questionnaire developed by the Principal Investigator for this purpose. Therapeutic alliance will also be measured with the Working Alliance Questionnaire/Helping Alliance Questionnaire.

Levels of inflammatory cytokines across the three timepoints (baseline, 8 weeks/post intervention and 3mth follow up) will also be examined using the saliva and serum collected from participants. A separate manuscript will be written related to the longitudinal examination of these cytokines.

TABLES AND FIGURES FOR THE MAIN PAPER

The proposed tables and figures for the main results are presented below. Table 1 will report key baseline characteristics of participants by patient group. Table 2 will report the primary and key secondary outcomes. Supplementary Figure 1 will be the CONSORT flowchart diagram. Depending on the journal publication restrictions, some of the above figures may be included in the main text, as supplementary figures or included in publications subsequent to the main publication.

3 REFERENCES

Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-II. San Antonio: The Psychological Corporation; 1996.

Spielberger CD, Gorsuch RL, Lushene RE. Manual for the State-Trait Anxiety Inventory. Palo Alto: Consulting Psychologists Press; 1970.

Kiropoulos, L., Kilpatrick, T., Kalincek, T. et al. Comparison of the effectiveness of a tailored cognitive behavioural therapy with a supportive listening intervention for depression in those newly diagnosed with multiple sclerosis (the ACTION-MS trial): protocol of an assessor-blinded, active comparator, randomised controlled trial. Trials 21, 100 (2020). https://doi.org/10.1186/s13063-019-4018-8

Table 1. Demographic and disease related data of participants

	CBT	SL	Total
Age, years			
Sex			
Female			
Male			
Ethnic background			
Australian			
UK (Britain, Scotland, Ireland)			
Asian			
North American (USA, Canada)			
Eastern Europe			
Southern Europe (Greece, Italy)			
Other			
Highest level of education completed			
Primary			
Secondary			
Trade, TAFE, or Diploma			
Undergraduate tertiary			
Postgraduate tertiary			
Marital status			
Single			
Partnered/Married			
Divorced/Widowed			
Employment status			
Unemployed			
Part time			
Full time			
Site			
Royal Melbourne Hospital			
Austin Hospital			
St Vincent's Hospital			
Alfred Hospital			
SR-EDSS <=3.5			
MS type			
Relapse remitting			
Progressive (primary/secondary)			
Months since first MS symptoms			
Months since MS diagnosis			
Taking MS disease modifying medication			
Yes			
How long on this medication in months			
Currently on anti-depressant/anxiety medication			
Yes			
Previously diagnosed with MDE/MDD			
Yes			
Previously diagnosed with anxiety disorder			

Yes			
COVID Vaccinations			
Yes			
Data are mean (SD), n (%). CBT = cognitive behavioural therapy. SL = supportive listening.			
***Table 1*: Demographic and disease related data of participants**			

Table 2. Group comparisons of outcomes of 8 weeks and 20 weeks

	CBT	SL	Effect size (95% CI)	p value
Patient reported outcomes				
>=10 points on BDI-II from baseline to 8wks				
BDI-II				
Baseline				
8 week				
20 week				
STAI				
Baseline				
8 week				
20 week				
MFIS-5				
Baseline				
8 weeks				
20 weeks				
PES				
Baseline				
8 weeks				
20 weeks				
MS-QOL 54 Physical				
Baseline				
8 weeks				
20 weeks				
MS-QOL 54 Mental				
Baseline				
8 weeks				
20 weeks				
EuroQoL-5 VAS				
Baseline				
8 weeks				
20 weeks				
PSSS				
Baseline				
8 weeks				
20 weeks				
Active coping				
Baseline				

8 weeks				
20 weeks				
RSA				
Baseline				
8 weeks				
20 weeks				
PSQI total				
Baseline				
8 weeks				
20 weeks				
PDQ-5				
Baseline				
Week 8				
Week 20				
ACHCS				
Baseline				
Week 8				
Week 20				
MSNQ				
Baseline				
Week 8				
Week 20				
Cognitive outcomes				
SDMT				
Baseline				
8 weeks				
20 weeks				
CVLT-II				
Baseline				
8 weeks				
20 weeks				
BVMT-R				
Baseline				
8 weeks				
20 weeks				

Table 2: Group comparison of outcomes at 8 weeks and 20 weeks

***Table 3*: Changes in SCID diagnoses at week 8 and week 20.**

	CBT		**SL**		***p* value**
MDD					
Baseline					
8 weeks					
20 weeks					
MDE					
Baseline					
8 weeks					
20 weeks					
Bipolar I disorder					

Baseline					
Week 8					
Week 20					
Bipolar II					
Baseline					
Week 8					
Week 20					
GAD					
Baseline					
Week 8					
Week 20					
SAD					
Baseline					
Week 8					
Week 20					
PD					
Baseline					
Week 8					
Week 20					
OCD					
Baseline					
Week 8					
Week 20					
PTSD					
Baseline					
Week 8					
Week 20					
AD due to GMC					
Baseline					
Week 8					
Week 20					
AD					
Baseline					
Week 8					
Week 20					
NASUD					
Baseline					
Week 8					
Week 20					
Data are n (%). CBT = cognitive behavioural therapy. SL = supportive listening.					
***Table 3*: Changes in SCID diagnoses at week 8 and week 20.**					

SUPPLEMENTARY MATERIAL

Supplementary Figure 1 – Standard CONSORT Flowchart