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Efficacy of cannabis-based Medicine Extract in slowing the disease pRogression of Amyotrophic Lateral sclerosis or motor neurone Disease (EMERALD): a randomised, double-blind, placebo-controlled study

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Running title: EMERALD Trial

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Word Count: 2585

Abstract

Introduction: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder with no known cure and with an average life expectancy of 3-5 years post diagnosis. The use of complementary and alternative medicine such as medicinal cannabis in search for a potential treatment or cure is common in ALS. Pre-clinical studies have demonstrated the efficacy of cannabinoids in extending the survival and slowing of progression in animal models of ALS. There are anecdotal reports of cannabis slowing disease progression in persons with ALS (pALS) and that cannabis alleviated symptoms of spasticity and pain. However, a clinical trial in pALS with these objectives has not been conducted.

Methods and analysis: The EMERALD trial is a randomised, double-blind, placebo-controlled cannabis trial in pALS at Gold Coast University Hospital, Australia. The investigational product will be a cannabis-based medicine extract (CBME) supplied by CannTrust Inc. with a high cannabidiol and low tetrahydrocannabinol concentration. A total of 30 pALS with probable or definite ALS diagnosis based on El Escorial criteria, aged between 25-75 years old and with at least 70% forced vital capacity (FVC) will be treated for 6 months. The primary objective of the study is to evaluate the efficacy of CBME compared to placebo in slowing the disease progression measured by differences in mean ALSFRS-R and FVC score between groups at the end of treatment. The secondary objectives are to evaluate the safety and tolerability of CBME by summarising adverse events, the effects of CBME on spasticity, pain, weight loss and quality of life assessed by differences in mean numeric rating scale in spasticity and pain, percentage of total weight loss and ALSSQOL-R questionnaire.

Ethics and dissemination: The study has been approved by the local Institutional Review Board. The results of this study will be published in a peer-reviewed journal.

Trial registration number: NCT03690791; Pre-results

Strengths and limitations of this study

- This study will evaluate the efficacy of cannabis in slowing ALS/MND progression.
- This study will also evaluate the efficacy of cannabis in improving the quality of life and in managing ALS/MND associated symptoms such as pain, spasticity and weight loss.
- This study is limited by not utilising a biomarker.
- This study has limitation in generalisibility as it only focuses in enrolling early stage ALS/MND patients, i.e. <2 years symptom onset.

Background

Amyotrophic lateral sclerosis (ALS), also known as motor neurone disease is a fatal neuromuscular disorder that results in the degeneration of the motor neurons in the cortex, brain stem and spinal cord[1, 2]. It is characterised by progressive weakness and wasting of skeletal muscles and loss of the ability to swallow or speak[2]. It commonly affects patients between 50 and 65 years of age[2-4]. The aetiology of ALS is largely unknown, although there is robust evidence demonstrating genetic or inherited causes accounting for 5 to 10% of the ALS population[5]. The average life expectancy from diagnosis is 3-5 years, but a small percentage of persons with ALS (pALS) may survive longer[2, 3].

More than 30 gene mutations have been linked to ALS such as SOD1, TARDBP (TDP-43), FUS/TLS and C9orf72[5]. Despite these advances, the pathophysiology of sporadic ALS remains unknown. Theories proposed include reduced glutamate uptake resulting in excitotoxicity, oxidative stress, mitochondrial dysfunction, neuro-inflammation and dysregulation of cellular metabolism[6].

The activation of the endocannabinoid system (ECS) has been demonstrated to reduce excitotoxicity, oxidative cell damage and neuro-inflammation[7, 8]. ECS is a vital physiologic neuro-modulatory system in human beings; it is involved in regulating homeostasis. ECS is widely expressed in different parts of the human body, particularly in the brain and spinal cord. ECS regulates physiologic processes such as pain, emotions, stress, neural development, inflammation, appetite and sleep cycles[9]. ECS has two major cannabinoid (CB) receptors - CB1 and CB2. CB1 receptors are extremely abundant in the nervous system whilst CB2 receptors are more present in immune cells[10].

Endogenous cannabinoids (cannabinoids that are intrinsic to humans) activate the ECS and have important roles in the naturalistic defence of the nervous system[11]. Anadamide (AEA) and 2-Arachidonoylglycerol (2-AG), known as endocannabinoids, are presumed to have key roles in slowing ALS progression. Endocannabinoids accumulated in the spinal cord of ALS mice with SOD1

mutations[12, 13] and acted as protective responses when the disease was progressing. It is therefore proposed that by introducing exogenous cannabinoids such as delta-9-tetrahydrocannabinol (THC) and/or cannabidiol (CBD), there is a possibility to slow ALS progression.

Pre-clinical studies have explored the relationship between ECS and ALS progression using transgenic mice with SOD1 and TDP-43 mutations[12, 14-17]. The administration of THC, an exogenous endocannabinoid that partially activates CB1 receptors[18] in transgenic SOD1 mice (either before or during their onset of symptom) reduced motor impairment by 6% and extended survival by 5%[15]. Similarly, the administration of WIN55,212-2 (a CB1/CB2 receptor agonist) in transgenic SOD1 mice after symptom onset significantly slowed disease progression[12]. The genetic ablation of fatty acid amide hydrolase enzymes, which eventually increases endocannabinoid levels, also slowed the disease progression and ameliorated disease signs[12].

Activating CB2 receptors is also believed to slow ALS progression[11]. CB2 receptors block beta-amyloid induced microglial activation which mediates excitotoxicity and neuronal damage[19]. To further support this claim, AM1241 (a selective CB2 receptor agonist) was administered to transgenic SOD1 mice after disease onset and demonstrated significant slowing of disease[14]. Also, the administration of AM1241 3mg/kg produced a 56% increase in survival interval and 11% increase in lifespan of SOD1 mice[16].

CB2 receptors also regulate human immune system. Neuro-inflammation is proposed as a possible mechanism in pathophysiology of ALS, hence regulating the immune system to counteract inflammation via CB2 receptors may positively modify disease progression[20]. The relationship of ECS in TDP-43, one of the genetic mutations causing ALS and frontotemporal dementia has been investigated[21]. Upregulation of CB2 receptors in the spinal cord of TDP-43 mice was demonstrated. This supports the premise that CB2 receptors are involved in the ALS pathogenesis possibly as an endogenous protective response.

There are case studies and anecdotal reports indicating improvement of symptoms in patients with confirmed ALS using cannabis[20]. In a survey of pALS, respondents admitted that cannabis moderately reduced disease associated symptoms such as appetite loss, depression, pain, spasticity and drooling[22].

Human clinical trials have investigated cannabinoids in pALS. However, these trials mainly focused on symptom-management rather than disease modification. One study showed symptomatic benefits in areas of sleep, appetite and spasticity[23]. It also demonstrated the safety of using THC in pALS. Another clinical trial explored the effects of THC (Marinol) in ALS patients with cramps[24], but the differences seen were not statistically significant. The authors pointed out that their results might be due to the small THC (Marinol) doses used and the treatment period being short (2 weeks), making it deficient to detect significant changes[24]. A more recent clinical trial has demonstrated significant reduction of ALS related spasticity with cannabinoids[25] and a larger clinical trial is underway.

Cannabinoids are largely regarded as safe for ALS population[23-25]. Given the potential therapeutic benefits further investigation is warranted. The most logical next step is to conduct a human clinical trial[26]. This study was designed to explore the efficacy of CBME in slowing ALS progression and improving symptom control.

Methods and Analysis

Study Overview

The EMERALD trial is a randomised, double-blind, placebo-controlled single centre study enrolling ALS patients with symptom onset within the last 2 years prior to randomisation. Patient recruitment will take place at Gold Coast University Hospital (GCUH), Australia. Recruitment of participants started in January 2019. All participants will be screened and if eligible will be enrolled in the trial. All participants are required to give written, informed consent prior to enrolment. Participants will

take either the study drug or placebo for 6 months. They will be followed up by face to face visit three monthly and phone call every month. It is anticipated that the study will take 2 years to complete (January 2019 to January 2021).

Study Objectives

The primary objective of the EMERALD trial is to evaluate the efficacy of CBME in slowing the disease progression of patients with ALS over 6 months of treatment using the ALS functional rating scale-revised (ALSFRS-R) and forced vital capacity (FVC).

The secondary objectives are to evaluate the safety and tolerability of CBME, its effects on spasticity, pain, weight loss and quality of life. Safety and tolerability will be assessed by collecting the number of adverse events, spasticity and pain scores using the numeric rating scale for spasticity (sNRS) and pain (pNRS), weight loss by calculating the percentage of total weight loss (%TWL), and quality of life using the ALS specific quality of life-revised (ALSSQOL-R) questionnaire.

This study will also explore the effects of CBME in cognition and behaviour of patients using the Edinburgh cognitive and behavioural ALS screen (ECAS). As an additional safety measure, risk of suicide will be assessed for all patients using the Columbia-suicide severity rating scale (C-SSRS). Additional clinical endpoints include death and inability to swallow.

Study Population

All consecutive patients that attend or are referred to GCUH Neurology ALS/MND Clinic with ALS/MND diagnosis and symptom onset within the last 2 years will be screened for eligibility. Patients fulfilling the inclusion criteria and none of the exclusion criteria will be asked to participate. The inclusion and exclusion criteria are summarised in Table 1.

Table 1 EMERALD Trial Inclusion and Exclusion Criteria

Inclusion Criteria

- Diagnosed with ALS/MND, either definite or probable according to the El Escorial revised criteria
- Male or female, 25-75 years old
- Onset of first symptom within the last 2 years
- Forced vital capacity (FVC) of at least 70% on baseline

Exclusion Criteria

- Participants who are bedridden
- Have used or taken cannabis or cannabinoid-based medications within 30 days of study entry
- History of any psychiatric disorder other than depression associated with their underlying condition including immediate family history of schizophrenia
- Any of the following: eGFR <30 mL/min/1.73m2, ejection fraction <35%, or ASL and ALT >5 X ULN
- Pregnant, lactating mother or female participant planning pregnancy during the study and for 30 days thereafter
- Unwilling to stop driving and operate heavy machineries

Study Intervention

Investigational Product

The investigational product is CBD oil formulated as a capsule and is supplied by CannTrust Inc., Canada. CannTrust Inc. is a licensed producer of medical grade cannabis. The investigational product contains 25mg of CBD and <2 mg of THC (+/-10%). Identical placebo capsules will contain only

medium chain triglyceride oil, which is the carrier for the study drug. There will be no cannabinoids or other cannabis-based compounds in the placebo.

The rationale for choosing this formulation of CBME relates to the entourage effect of cannabinoids. When administered together, cannabinoids modulate or enhance the effects of the various components, and reduction of psychoactive effects associated with cannabis can be seen[27]. THC and CBD are two of the well understood cannabinoids out of the 60 constituents of the cannabis plant[28]. THC is the major psychoactive constituent in cannabis whilst CBD is known to have neuroprotective effects and is non-intoxicating, but has anti-anxiety and anti-psychotic activity. CBD modulates the activation of cannabinoid receptors[27] and may counteract the psychoactive effects of THC[29]. A high CBD low THC ratio was chosen for this study not only to mitigate the psychoactive effects of THC but to leverage the neuroprotective potentials of CBD.

Dose and Mode of Administration

The medication is to be taken orally daily for 6 months. The appropriate dose for each participant is determined by going through a titration period on the first 14 days of study. The titration regimen is described in Table 2.

Table 2. Dose titration regimen for investigational product

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Week 1	<4mg THC 50mg CBD	<6mg THC 75mg CBD	<8mg THC 100mg CBD	10<mg THC 125mg CBD	<12mg THC 150mg CBD	<14mg THC 175mg CBD	<16mg THC 200mg CBD
	am: 25 night: 25	am: 25 noon: 25 night: 25	am: 25 noon: 25 night: 25 x2	am: 25 noon: 25 x2 night: 25 x2	am: 25 noon: 25 x2 night: 25 x3	am: 25 noon: 25 x2 night: 25 x4	am: 25 noon: 25 x2 night: 25 x5
	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Week 2	<18mg THC 225mg CBD	<20mg THC 250mg CBD	<22mgTHC 275mg CBD	<24mg THC 300mg CBD	<26mg THC 325mg CBD	<28mg THC 350mg CBD	<30mg THC 375mg CBD

	am: (25) x2 noon: (25) x2 night: (25) x5	am: (25) x2 noon: (25) x2 night: (25) x6	am: (25) x2 noon: (25) x2 night: (25) x7	am: (25) x2 noon: (25) x2 night: (25) x8	am: (25) x2 noon: (25) x3 night: (25) x8	am: (25) x2 noon: (25) x4 night: (25) x8	am: (25) x3 noon: (25) x4 night: (25) x8

(25) 25mg CBD and <2mg THC in a capsule

Titration Period

A titration period is required to reach the optimal dose for each participant. Participants will begin taking an initial total dose of 50 mg of CBD and <4 mg THC or placebo. The dose will increase gradually for each participant depending on the effect of the study drug and the tolerability of each participant. The participants will continue titration until an undesired side effect is experienced or maximum dose of 375mg of CBD and <30mg of THC (+/-10%) is achieved. If an undesired side effect occurs, the participant will be tapered down to the last dose where no side-effects were reported.

The titration regimen for this study was based on the principle of start low and go slow[30]. Patients taking the approved cannabinoid Sativex (Nabiximols) commence medication using a titration scheme for up to 2 weeks to determine optimal drug dose. The pharmacokinetic variability of Sativex is high between individuals, but low within individuals[31].

After the titration phase, participants will enter the maintenance period. They will continue taking the titrated dose for the remainder of the study.

Study Procedures

Thirty (30) ALS/MND patients will be randomised in a 1:1 ratio to receive CannTrust CBD Oil or placebo (both in capsules). Patients will be stratified based on their age: <65 and >65 years old. The treatment duration is 6 months with one-month safety follow up. Participants will be checked every

month either face to face or via telephone and relevant data will be collected. Data of patients will be stored in Research Electronic Data Capture (REDCap) at baseline and follow up visits. Clinical data include demographics, medical history, El Escorial diagnosis, ALSFR-R score, date of symptom onset and the site, physical examination, vital signs, laboratory tests, weight and height, concomitant medications, adverse events, and study related questionnaires. Study procedures are summarised in Figure 1.

Randomisation

The randomisation command ralloc in Stata 9.0 (College Station, TX, USA) will be used to perform stratified randomisation in this study (>65 and <65 years old). Gold Coast Health biostatistician will generate stratified randomisation code blocks to ensure approximate balance (1:1) between the two arms (treatment and placebo). These blocks will be personally handed over or sent privately to trial pharmacists in a password protected file. The allocation code blocks will be accessed only by trial pharmacists and will be stored in a password protected computer. Trial pharmacists and biostatistician will not be involved in any other aspect of the study.

Blinding

To ensure blinding of investigators and participants to study treatment, the study drug or placebo will be provided in similar packaging, label and appearance. Study drug and placebo will be labelled with a unique label letter that will be used to assign treatment to the patient but will not indicate treatment allocation to the investigators or participants. No member of the study team and their extended staff will have access to the randomisation scheme during the conduct of the study, except for the trial pharmacists and biostatistician.

Sample Size

To detect a clinically relevant difference of 3.0 points on the ALSFRS-R scale with a power of 90% at a significance level of 5% based on a two-sample t-test to compare treatment groups, it was calculated that a total sample size of 30 participants was required (G* Power version 3.1.9.2). This assumed a standard deviation of 2.4 points in each group based on the results of the Edaravone MCI-186-19 trial[32].

Statistical Analyses

Efficacy outcomes will be analysed on an intention-to-treat basis. Primary outcomes will be analysed by comparing the difference of mean ALSFRS-R and Forced Vital Capacity scores between groups at the end of the treatment period using linear regression. Statistical significance will be set at a two-sided level of 0.05. This simple analysis will be extended to include covariates such as gender and ALS onset site through linear regression.

Secondary outcomes will be analysed using with the same method as primary outcomes. Clinical endpoints (death and inability to swallow) will be assessed in a time to event analysis using Kaplan-Meier plots, log-rank tests and Cox proportional hazard analyses.

Safety data will be collected and summarised from baseline to Day 210. Safety data will be listed by subject and summarised by treatment (active or placebo) using the number of subjects (n and percent) with events/abnormalities for categorical data. Nature and number of adverse events will be analysed using poisson test.

Exploratory outcome will be analysed by comparing the difference of mean ECAS scores between groups at end of treatment using linear regression.

Patient and Public Involvement

The research question was informed by MND patients asking whether cannabis has potential treatment effects. Neither patients nor the public were directly involved in the selection of outcome measures, design and implementation of the study.

Ethics and dissemination

EMERALD trial is being conducted according to Good Clinical Practice and the Declaration of Helsinki. This study has been approved by the local Institutional Review Board (Gold Coast Hospital and Health Service Ethics Committee – Reference No: HREC/17/QGC/293) in April 2018. Study monitoring will be conducted by the Gold Coast Hospital and Health Service Research Directorate Office. To ensure patient safety, DSMB will meet regularly to review adverse events and safety data. DSMB is composed of academics and clinicians including biostatistician, all of whom are not directly involved in the study conduct. Patients are advised that they can withdraw from the study at any time. This study has been registered at clinicaltrials.gov (NCT03690791). Study results will be presented at scientific conferences and published in a peer-reviewed journal.

Current study status

The EMERALD trial has begun enrolling patients in January 2019. We expect the trial to be completed in January 2021.

Figure Legends

Figure 1. Summary of study procedures

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Authors Contributors. BU and AS conceived and designed this study. BU drafted the study protocol and organised the study implementation. AS, SB, RB, ER refined the study protocol. BU drafted the manuscript. All authors approved the final version of the manuscript.

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Disclaimer. The funders are not involved in the study design, conduct, analysis and reporting of this study.

Competing Interests. The investigational product has been provided by CannTrust Inc.

Patient Consent. Obtained.

Ethics Approval. This study has been approved by Institutional Review Board (Gold Coast Hospital and Health Service Human Research Ethics Committee).

Provenance and peer review. Not commissioned; externally peer reviewed.

Data sharing statement. Additional data can be requested from the authors. However, the decision to disclose data is solely based from authors' discretion and funding agency.

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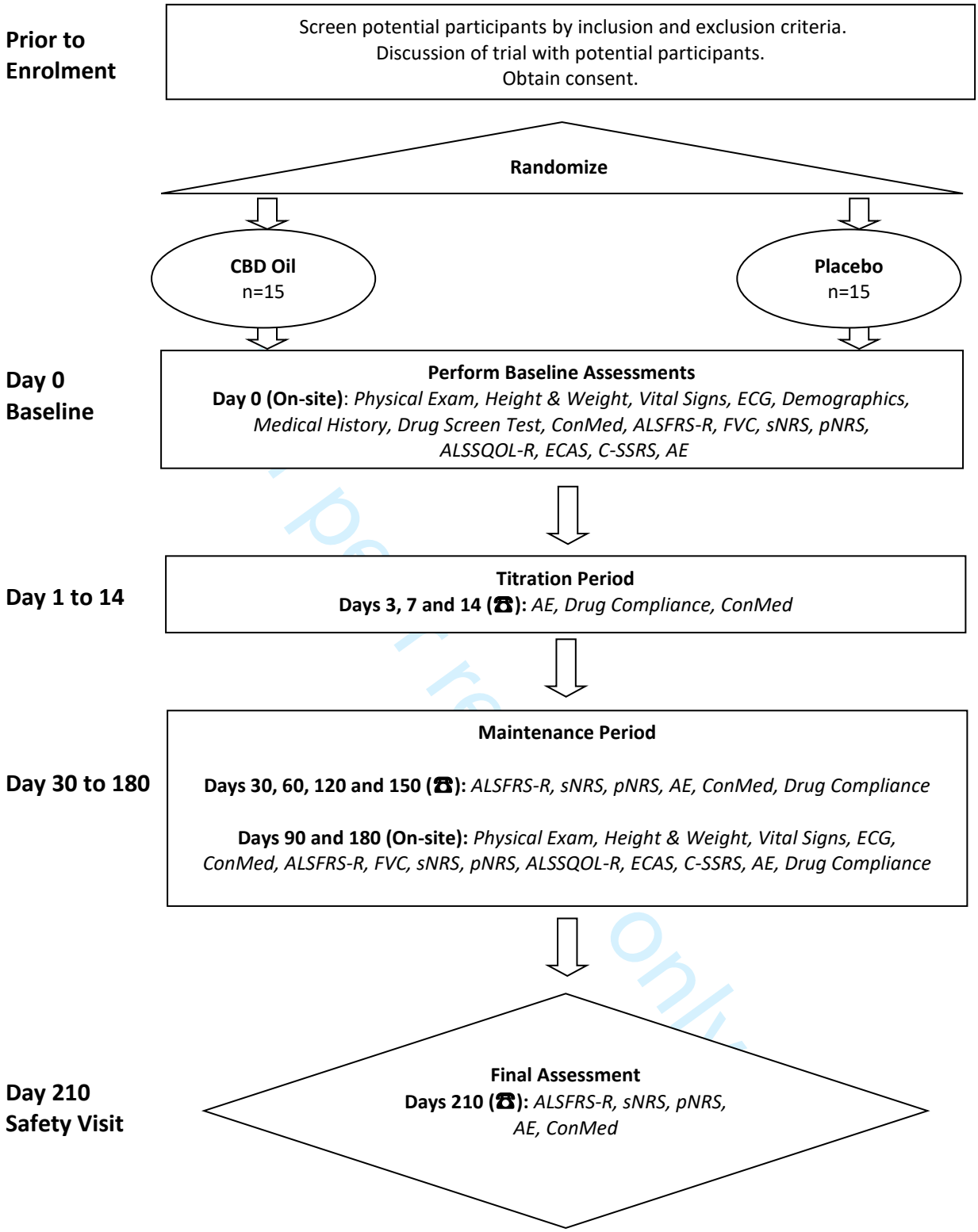
Prior to Enrolment
Screen potential participants by inclusion and exclusion criteria.
Discussion of trial with potential participants.
Obtain consent.
Randomize
CBD Oil
n=15
Placebo
n=15
Day 0 Baseline
Perform Baseline Assessments
Day 0 (On-site): Physical Exam, Height & Weight, Vital Signs, ECG, Demographics, Medical History, Drug Screen Test, ConMed, ALSFRS-R, FVC, sNRS, pNRS, ALSSQOL-R, ECAS, C-SSRS, AE
Day 1 to 14
Titration Period
Days 3, 7 and 14 (☎): AE, Drug Compliance, ConMed
Day 30 to 180
Maintenance Period
Days 30, 60, 120 and 150 (☎): ALSFRS-R, sNRS, pNRS, AE, ConMed, Drug Compliance
Days 90 and 180 (On-site): Physical Exam, Height & Weight, Vital Signs, ECG, ConMed, ALSFRS-R, FVC, sNRS, pNRS, ALSSQOL-R, ECAS, C-SSRS, AE, Drug Compliance
Day 210 Safety Visit
Final Assessment
Days 210 (☎): ALSFRS-R, sNRS, pNRS, AE, ConMed

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-6
	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	10-11
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-10
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	11
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	11
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	11
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	11-12
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	12

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	N/A
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	N/A
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	1-2
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	N/A
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	13
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

A study protocol for a randomised, double-blind, placebo-controlled study evaluating the Efficacy of cannabis-based Medicine Extract in slowing the disease pRogression of Amyotrophic Lateral sclerosis or motor neurone Disease: the EMERALD trial

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A study protocol for a randomised, double-blind, placebo-controlled study evaluating the Efficacy of cannabis-based Medicine Extract in slowing the disease pRogression of Amyotrophic Lateral sclerosis or motor neurone Disease: the EMERALD trial

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Running title: EMERALD Trial

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Word Count: 3203

Abstract

Introduction: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder with no known cure and with an average life expectancy of 3-5 years post diagnosis. The use of complementary and alternative medicine such as medicinal cannabis in search for a potential treatment or cure is common in ALS. Pre-clinical studies have demonstrated the efficacy of cannabinoids in extending the survival and slowing of progression in animal models of ALS. There are anecdotal reports of cannabis slowing disease progression in persons with ALS (pALS) and that cannabis alleviated symptoms of spasticity and pain. However, a clinical trial in pALS with these objectives has not been conducted.

Methods and analysis: The EMERALD trial is a randomised, double-blind, placebo-controlled cannabis trial in pALS at Gold Coast University Hospital, Australia. The investigational product will be a cannabis-based medicine extract (CBME) supplied by CannTrust Inc. with a high cannabidiol and low tetrahydrocannabinol concentration. A total of 30 pALS with probable or definite ALS diagnosis based on El Escorial criteria with symptom duration of <2 years, age between 25 and 75 and with at least 70% forced vital capacity (FVC) will be treated for 6 months. The primary objective of the study is to evaluate the efficacy of CBME compared to placebo in slowing the disease progression measured by differences in mean ALS Functional Rating Scale-Revised (ALSFRS-R) and FVC score between groups at the end of treatment. The secondary objectives are to evaluate the safety and tolerability of CBME by summarising adverse events, the effects of CBME on spasticity, pain, weight loss and quality of life assessed by differences in mean numeric rating scale in spasticity and pain, percentage of total weight loss and ALSSQOL-R questionnaire.

Ethics and dissemination: The study has been approved by the local Institutional Review Board. The results of this study will be published in a peer-reviewed journal.

Trial registration number: NCT03690791; Pre-results

Strengths and limitations of this study

- This study will evaluate the efficacy of cannabis in slowing ALS/MND progression.
- This study will also evaluate the efficacy of cannabis in improving the quality of life and in managing ALS/MND associated symptoms such as pain, spasticity and weight loss.
- This study is limited by not utilising a biomarker.
- This study has limitation in generalisibility as it only focuses in enrolling early stage ALS/MND patients, i.e. <2 years symptom onset.

Background

Amyotrophic lateral sclerosis (ALS), also known as motor neurone disease is a fatal neuromuscular disorder that results in the degeneration of the motor neurons in the cortex, brain stem and spinal cord[1, 2]. It is characterised by progressive weakness and wasting of skeletal muscles and loss of the ability to swallow or speak[2]. It commonly affects patients between 50 and 65 years of age[2-4]. The aetiology of ALS is largely unknown, although there is robust evidence demonstrating genetic or inherited causes accounting for 5 to 10% of the ALS population[5]. The average life expectancy from diagnosis is 3-5 years, but a small percentage of persons with ALS (pALS) may survive longer[2, 3].

More than 30 gene mutations have been linked to ALS such as SOD1, TARDBP (TDP-43), FUS/TLS and C9orf72[5]. Despite these advances, the pathophysiology of sporadic ALS remains unknown. Theories proposed include reduced glutamate uptake resulting in excitotoxicity, oxidative stress, mitochondrial dysfunction, neuro-inflammation and dysregulation of cellular metabolism[6].

The activation of the endocannabinoid system (ECS) has been demonstrated to reduce excitotoxicity, oxidative cell damage and neuro-inflammation[7, 8]. ECS is a vital physiologic neuro-modulatory system in human beings; it is involved in regulating homeostasis. ECS is widely expressed in different parts of the human body, particularly in the brain and spinal cord. ECS regulates physiologic processes such as pain, emotions, stress, neural development, inflammation, appetite and sleep cycles[9]. ECS has two major cannabinoid (CB) receptors - CB1 and CB2. CB1 receptors are extremely abundant in the nervous system whilst CB2 receptors are more present in immune cells[10].

Endogenous cannabinoids (cannabinoids that are intrinsic to humans) activate the ECS and have important roles in the naturalistic defence of the nervous system[11]. Anadamide (AEA) and 2-Arachidonoylglycerol (2-AG), known as endocannabinoids, are presumed to have key roles in slowing ALS progression. Endocannabinoids accumulated in the spinal cord of ALS mice with SOD1

mutations[12, 13] and acted as protective responses when the disease was progressing. It is therefore proposed that by introducing exogenous cannabinoids such as delta-9-tetrahydrocannabinol (THC) and/or cannabidiol (CBD), there is a possibility to slow ALS progression.

Pre-clinical studies have explored the relationship between ECS and ALS progression using transgenic mice with SOD1 and TDP-43 mutations[12, 14-17]. The administration of THC, an exogenous endocannabinoid that partially activates CB1 receptors[18] in transgenic SOD1 mice (either before or during their onset of symptom) reduced motor impairment by 6% and extended survival by 5%[15]. Similarly, the administration of WIN55,212-2 (a CB1/CB2 receptor agonist) in transgenic SOD1 mice after symptom onset significantly slowed disease progression[12]. The genetic ablation of fatty acid amide hydrolase enzymes, which eventually increases endocannabinoid levels, also slowed the disease progression and ameliorated disease signs[12].

Activating CB2 receptors is also believed to slow ALS progression[11]. CB2 receptors block beta-amyloid induced microglial activation which mediates excitotoxicity and neuronal damage[19]. To further support this claim, AM1241 (a selective CB2 receptor agonist) was administered to transgenic SOD1 mice after disease onset and demonstrated significant slowing of disease[14]. Also, the administration of AM1241 3mg/kg produced a 56% increase in survival interval and 11% increase in lifespan of SOD1 mice[16].

CB2 receptors also regulate human immune system. Neuro-inflammation is proposed as a possible mechanism in pathophysiology of ALS, hence regulating the immune system to counteract inflammation via CB2 receptors may positively modify disease progression[20]. The relationship of ECS in TDP-43, one of the genetic mutations causing ALS and frontotemporal dementia has been investigated[21]. Upregulation of CB2 receptors in the spinal cord of TDP-43 mice was demonstrated. This supports the premise that CB2 receptors are involved in the ALS pathogenesis possibly as an endogenous protective response.

There are case studies and anecdotal reports indicating improvement of symptoms in patients with confirmed ALS using cannabis[20]. In a survey of pALS, respondents admitted that cannabis moderately reduced disease associated symptoms such as appetite loss, depression, pain, spasticity and drooling[22].

Human clinical trials have investigated cannabinoids in pALS. However, these trials mainly focused on symptom-management rather than disease modification. One study showed symptomatic benefits in areas of sleep, appetite and spasticity[23]. It also demonstrated the safety of using THC in pALS. Another clinical trial explored the effects of THC (Marinol) in ALS patients with cramps[24], but the differences seen were not statistically significant. The authors pointed out that their results might be due to the small THC (Marinol) doses used and the treatment period being short (2 weeks), making it deficient to detect significant changes[24]. A more recent clinical trial has demonstrated significant reduction of ALS related spasticity with cannabinoids[25] and a larger clinical trial is underway.

Cannabinoids are largely regarded as safe for ALS population[23-25]. Given the potential therapeutic benefits further investigation is warranted. The most logical next step is to conduct a human clinical trial[26]. This study was designed to explore the efficacy of CBME in slowing ALS progression and improving symptom control.

Methods and Analysis

Study Overview

The EMERALD trial is a randomised, double-blind, placebo-controlled single centre study enrolling ALS patients with symptom onset within the last 2 years prior to randomisation. Patient recruitment will take place at Gold Coast University Hospital (GCUH), Australia. Recruitment of participants started in January 2019. All participants will be screened and if eligible will be enrolled in the trial. All participants are required to give written, informed consent prior to enrolment. Participants will take

either the study drug or placebo for 6 months. They will be followed up by face to face visit three monthly and phone call every month. It is anticipated that the study will take 2.5 years to complete (January 2019 to June 2021).

Study Objectives

The primary objective of the EMERALD trial is to evaluate the efficacy of CBME in slowing the disease progression of patients with ALS over 6 months of treatment using the ALS functional rating scale-revised (ALSFRS-R) and forced vital capacity (FVC).

The secondary objectives are to evaluate the safety and tolerability of CBME, its effects on spasticity, pain, weight loss and quality of life. Safety and tolerability will be assessed by collecting the number of adverse events, spasticity and pain scores using the numeric rating scale for spasticity (sNRS) and pain (pNRS), weight loss by calculating the percentage of total weight loss (%TWL), and quality of life using the ALS specific quality of life-revised (ALSSQOL-R) questionnaire.

This study will also explore the effects of CBME in cognition and behaviour of patients using the Edinburgh cognitive and behavioural ALS screen (ECAS). As an additional safety measure, risk of suicide will be assessed for all patients using the Columbia-suicide severity rating scale (C-SSRS). Additional clinical endpoints include death and inability to swallow.

Study Population

All consecutive patients that attend or are referred to GCUH Neurology ALS/MND clinic with ALS/MND diagnosis and symptom onset within the last 2 years, age between 25 and 75, and recent Forced Vital Capacity of at least 70% will be screened for eligibility. The age range (25-75 years old) was chosen because cannabis use may cause memory deficits for developing brain (up to 24 years old)

[27,28] and there is limited data on the safety of cannabis in the elderly. The inclusion and exclusion criteria are summarised in Table 1.

Prior randomisation, the study team will ask each patient if they have taken cannabis or cannabis-based medication within the last 30 days. Additionally, each patient will undergo a THC urine test prior randomisation. Patients who test positive for THC will be excluded.

Table 1 EMERALD Trial Inclusion and Exclusion Criteria

Inclusion Criteria

- Diagnosed with ALS/MND, either definite or probable according to the El Escorial revised criteria
- Male or female, 25-75 years old
- Onset of first symptom within the last 2 years
- Forced vital capacity (FVC) of at least 70% on baseline

Exclusion Criteria

- Participants who are bedridden
- Have used or taken cannabis or cannabinoid-based medications within 30 days of study entry
- History of any psychiatric disorder other than depression associated with their underlying condition including immediate family history of schizophrenia
- Any of the following: eGFR <30 mL/min/1.73m2, ejection fraction <35%, or ASL and ALT >5 X ULN
- Pregnant, lactating mother or female participant planning pregnancy during the study and for 30 days thereafter
- Unwilling to stop driving and operate heavy machineries

Study Intervention

Investigational Product

The investigational product is CBD oil formulated as a capsule and is supplied by CannTrust Inc., Canada. CannTrust Inc. is a licensed producer of medical grade cannabis. The investigational product contains 25mg of CBD and <2 mg of THC (+/-10%). Identical placebo capsules will contain only medium chain triglyceride oil, which is the carrier for the study drug. There will be no cannabinoids or other cannabis-based compounds in the placebo.

A systematic review of cannabinoids in ALS murine models[29] demonstrated the efficacy of cannabinoids in prolonging survival of SOD1-G93A mice. A high CBD, low THC formulation was chosen because this most closely resembles the preparation used in an animal model study[30] which demonstrated prolonged survival.

Additionally, the rationale for choosing a high CBD low THC formulation relates to the entourage effect of cannabinoids. When administered together, cannabinoids modulate or enhance the effects of the various components, and reduction of psychoactive effects associated with cannabis can be seen[31]. THC and CBD are two of the well understood cannabinoids out of the 60 constituents of the cannabis plant[32]. THC is the major psychoactive constituent in cannabis whilst CBD is known to have neuroprotective effects and is non-intoxicating, but has anti-anxiety and anti-psychotic activity. CBD modulates the activation of cannabinoid receptors[31] and may counteract the psychoactive effects of THC[33]. A high CBD low THC ratio was chosen for this study not only to mitigate the psychoactive effects of THC but to leverage the neuroprotective potentials of CBD.

Dose and Mode of Administration

The maximum dose was determined by balancing the expected dose range for therapeutic effects with doses associated with undesired side effects. The CBD oil to be used in this study consists of a 25mg:<2mg ratio of CBD and THC where the THC component is known to be the agent causing potential psychoactive side effects. The therapeutic range of CBD/THC products (for social anxiety disorder, epilepsy, and insomnia) was found to be 150-600mg of CBD/day[34]. This equates to <12mg to <48mg of THC of the study drug. However, as little as 2.5-3.0mg of pure THC in a single bolus has been reported to cause psychoactive effects in cannabis naïve patients[35]. We expect to be able to avoid low-dose THC psychoactive side effects as 1.) THC is combined with CBD which is known to mitigate the psychoactive effects of THC[36] and 2.) the daily dose will be given bid or tds (split between two doses 8-12 hours apart). In addition, we will employ the "start low go slow" rationale to increase the dose into the likely therapeutic range thus allowing for adaptation by patients to potential side effects. The *Clinical Guidance: for the use of medicinal cannabis products in Queensland*[35], where this trial is being conducted, suggests a maximum dose of 32.4mg/day of THC for Sativex and 40mg of THC for Marinol. The investigators set <30mg of THC as the maximum dose for our trial. This is a conservative maximum dose but is still expected to produce therapeutic results.

The medication is to be taken orally daily for 6 months. The appropriate dose for each participant is determined by going through a titration period on the first 14 days of study. The titration regimen is described in Table 2.

Table 2. Dose titration regimen for investigational product

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Week 1	<4mg THC 50mg CBD	<6mg THC 75mg CBD	<8mg THC 100mg CBD	10<mg THC 125mg CBD	<12mg THC 150mg CBD	<14mg THC 175mg CBD	<16mg THC 200mg CBD
	am: 25 night: 25	am: 25 noon: 25 night: 25	am: 25 noon: 25 night: 25 x2	am: 25 noon: 25 x2 night: 25 x2	am: 25 noon: 25 x2 night: 25 x3	am: 25 noon: 25 x2 night: 25 x4	am: 25 noon: 25 x2 night: 25 x5
	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14

	<18mg THC 225mg CBD	<20mg THC 250mg CBD	<22mgTHC 275mg CBD	<24mg THC 300mg CBD	<26mg THC 325mg CBD	<28mg THC 350mg CBD	<30mg THC 375mg CBD
Week 2	am: (25) x2 noon: (25) x2 night: (25) x5	am: (25) x2 noon: (25) x2 night: (25) x6	am: (25) x2 noon: (25) x2 night: (25) x7	am: (25) x2 noon: (25) x2 night: (25) x8	am: (25) x2 noon: (25) x3 night: (25) x8	am: (25) x2 noon: (25) x4 night: (25) x8	am: (25) x3 noon: (25) x4 night: (25) x8

(25) 25mg CBD and <2mg THC in a capsule

Titration Period

A titration period is required to reach the optimal dose for each participant. Participants will begin taking an initial total dose of 50 mg of CBD and <4 mg THC or placebo. The dose will increase gradually for each participant depending on the effect of the study drug and the tolerability of each participant. The participants will continue titration until an undesired side effect is experienced or maximum dose of 375mg of CBD and <30mg of THC (+/-10%) is achieved. If an undesired side effect occurs, the participant will be tapered down to the last dose where no side-effects were reported.

The titration regimen for this study was based on the principle of start low and go slow[37]. Patients taking the approved cannabinoid nabiximols (Sativex) commence medication using a titration scheme for up to 2 weeks to determine optimal drug dose. The pharmacokinetic variability of nabiximols is high between individuals, but low within individuals[38].

After the titration phase, participants will enter the maintenance period. They will continue taking the titrated dose for the remainder of the study.

Study Procedures

Thirty (30) ALS/MND patients will be randomised in a 1:1 ratio to receive CannTrust CBD Oil or placebo (both in capsules). Patients will be stratified based on their age: <65 and >65 years old. The

treatment duration is 6 months with one-month safety follow up. Participants will be checked every month either face to face or via telephone and relevant data will be collected. Data of patients will be stored in Research Electronic Data Capture (REDCap) at baseline and follow up visits. Clinical data include demographics, medical history, El Escorial diagnosis, ALSFR-R score, date of symptom onset and the site, physical examination, vital signs, laboratory tests, weight and height, concomitant medications, adverse events, drug compliance and study related questionnaires. Participants will be advised to avoid opiates, alcohol, and sleep medications due to cumulative drug effects of cannabis. Participants will also be advised not to drive vehicles and operate heavy machineries while in the trial. Study procedures are summarised in Figure 1.

Randomisation

The randomisation command ralloc in Stata 9.0 (College Station, TX, USA) will be used to perform stratified randomisation in this study (>65 and <65 years old). Gold Coast Health biostatistician will generate stratified randomisation code blocks to ensure approximate balance (1:1) between the two arms (treatment and placebo). These blocks will be personally handed over or sent privately to trial pharmacists in a password protected file. The allocation code blocks will be accessed only by trial pharmacists and will be stored in a password protected computer. Trial pharmacists and biostatistician will not be involved in any other aspect of the study.

Blinding

To ensure blinding of investigators and participants to study treatment, the study drug or placebo will be provided in identical packaging and label. Due to some natural variability in the colour of the study drug, which is batch dependent, the colour of the placebo has been matched to be the same as the average colour of the study drug. Study drug and placebo will be labelled with a unique label letter that will be used to assign treatment to the patient but will not indicate treatment allocation to the

investigators or participants. No member of the study team and their extended staff, except for the trial pharmacists and biostatistician, will have access to the randomisation scheme during the conduct of the study. In the event of a medical emergency, where breaking the blind is required to provide medical care to the participant, the investigator will obtain the treatment assignment from trial pharmacists.

Sample Size

To detect a clinically relevant difference of 3.0 points on the ALSFRS-R scale with a power of 90% at a significance level of 5% based on a two-sample t-test to compare treatment groups, it was calculated that a total sample size of 30 participants was required (G* Power version 3.1.9.2). Sample size estimation was based on results from the Edaravone MCI-186-19 trial[39] as their study population is similar to the target population of this trial, i.e. <2 years since onset of first ALS symptom. A standard deviation result of 2.4 units on the ALSFRS-R scale was chosen as it represented the largest pre-treatment estimate from each of the treatment and control groups of Edaravone MCI-186-19 trial[39] prior to observation or at baseline.

Statistical Analyses

Efficacy outcomes will be analysed on an intention-to-treat basis. Primary outcomes will be analysed by comparing the difference of mean ALSFRS-R and Forced Vital Capacity scores between groups at the end of the treatment period using linear regression. Statistical significance will be set at a two-sided level of 0.05. This simple analysis will be extended to include covariates such as gender and ALS onset site through linear regression.

Secondary outcomes will be analysed using with the same method as primary outcomes. Clinical endpoints (death and inability to swallow) will be assessed in a time to event analysis using Kaplan-Meier plots, log-rank tests and Cox proportional hazard analyses.

Safety data will be collected and summarised from baseline to Day 210. Safety data will be listed by subject and summarised by treatment (active or placebo) using the number of subjects (n and percent) with events/abnormalities for categorical data. Nature and number of adverse events will be analysed using poisson test.

Exploratory outcome will be analysed by comparing the difference of mean ECAS scores between groups at end of treatment using linear regression.

Patient and Public Involvement

The research question was informed by MND patients asking whether cannabis has potential treatment effects. Neither patients nor the public were directly involved in the selection of outcome measures, design and implementation of the study.

Ethics and dissemination

EMERALD trial is being conducted according to Good Clinical Practice and the Declaration of Helsinki. This study has been approved by the local Institutional Review Board (Gold Coast Hospital and Health Service Ethics Committee – Reference No: HREC/17/QGC/293) in April 2018. This study is currently on Protocol Version 5.1 dated 31st March 2019. Study monitoring will be conducted by the Gold Coast Hospital and Health Service Research Directorate Office. To ensure patient safety, DSMB will meet regularly to review adverse events and safety data. DSMB is composed of academics and clinicians including biostatistician, all of whom are not directly involved in the study conduct. Study investigators will consent participants. The consent form includes information about the study, the risks and benefits of joining the trial, study visits, collection and reporting of adverse events, and compensation for trial-related harms. Participants are advised that they can withdraw from the study at

any time. This study has been registered at clinicaltrials.gov (NCT03690791). Study results will be presented at scientific conferences and published in a peer-reviewed journal.

Current study status

The EMERALD trial has begun enrolling patients in January 2019. We expect the trial to be completed in June 2021.

Figure Legends

Figure 1. Summary of study procedures

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Authors Contributors. BU and AS conceived and designed this study. BU drafted the study protocol and organised the study implementation. AS, SB, RB, ER refined the study protocol. BU drafted the manuscript. All authors approved the final version of the manuscript.

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Disclaimer. The funders are not involved in the study design, conduct, analysis and reporting of this study.

Competing Interests. The investigational product has been provided by CannTrust Inc. Canntrust Inc. has no any involvement in this study (including but not limited to planning, analysis, or write-up or publication).

Patient Consent. Obtained.

Ethics Approval. This study has been approved by Institutional Review Board (Gold Coast Hospital and Health Service Human Research Ethics Committee).

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Data sharing statement. Additional data can be requested from the authors. However, the decision to disclose data is solely based from authors' discretion and funding agency.

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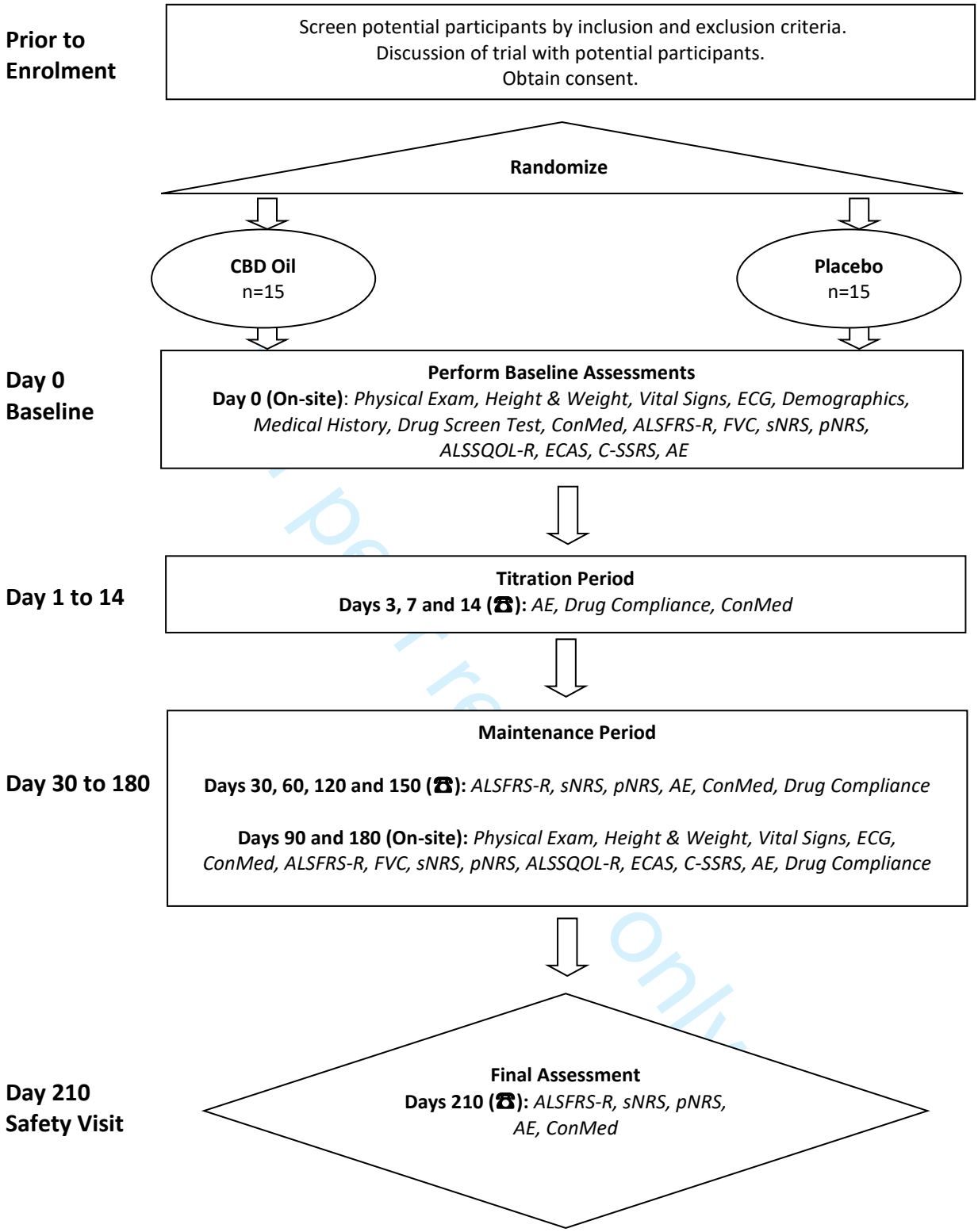
Prior to Enrolment
Screen potential participants by inclusion and exclusion criteria.
Discussion of trial with potential participants.
Obtain consent.
Randomize
CBD Oil
n=15
Placebo
n=15
Day 0 Baseline
Perform Baseline Assessments
Day 0 (On-site): Physical Exam, Height & Weight, Vital Signs, ECG, Demographics, Medical History, Drug Screen Test, ConMed, ALSFRS-R, FVC, sNRS, pNRS, ALSSQOL-R, ECAS, C-SSRS, AE
Day 1 to 14
Titration Period
Days 3, 7 and 14 (☎): AE, Drug Compliance, ConMed
Day 30 to 180
Maintenance Period
Days 30, 60, 120 and 150 (☎): ALSFRS-R, sNRS, pNRS, AE, ConMed, Drug Compliance
Days 90 and 180 (On-site): Physical Exam, Height & Weight, Vital Signs, ECG, ConMed, ALSFRS-R, FVC, sNRS, pNRS, ALSSQOL-R, ECAS, C-SSRS, AE, Drug Compliance
Day 210 Safety Visit
Final Assessment
Days 210 (☎): ALSFRS-R, sNRS, pNRS, AE, ConMed

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3, 15
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	14
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 16
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6-7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7-8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9-10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7, 13

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12-13
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11-12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13-14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13-14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14 (Study monitoring)
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15

	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A (Authorship guideline as per ICMJE)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.