THE UNIVERSITY of EDINBURGH

MND–SMART
Clinical trials for MND

EUAN MACDONALD CENTRE
Vital research into motor neuron disease

MND SMART South Wales

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Trial design

- **S**ystematic **M**ulti-**A**rm **R**andomised **T**rial
- Double blind
- Testing three drugs and a placebo
- Aim to recruit 800 adult pwMND nationally
- 19 sites currently open in the UK
- 400 patients recruited as off October 2022
- Duration 7 years (Until 113 deaths in placebo group or 150 pt per group have 18 mo follow up data - whichever is later) or if predefined stopping criteria are met

Aim

- To see if drugs used to treat other medical conditions can slow the progression of MND
- To measure how well the study drug is working by looking at changes in function over 18 months and survival of patients in study
- Establish the safety profile of the IMPs in pwMND

IMP

Memantine:

- A drug used to improve the memory in patients with Alzheimer's dementia.
- Reducing a brain chemical transmitter called glutamate.
- May slow the damage to brain cells in pwMND.

Trazadone:

- Used widely in the treatment of low mood.
- In animal studies, protect brain cell death by slowing production of faulty proteins.

IMP

Amantadine

- A drug licensed for use in the management of Parkinson's disease.
- Also used in treatment of fatigue in MS and as an antiviral medicine in the treatment of Type A influenza
- In vitro testing -Treatment of motor neurons with amantadine significantly reduced both number and size of TDP-43 a protein recognised as an important in pathogenic mechanism of neurodegenerative diseases.
- NB: Not yet recruiting to this arm awaiting approval

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Outcome measures used in MND SMART

- Changes in function (ALSFRS)
- Time to Kings Stage 4a (Nutritional failure)
- Time to kings Stage 4b (Respiratory failure)
- Change in cognitive function via (ECAS)
- Changes in respiratory function (FVC)
- Changes in anxiety and depression (HADS)
- Changes in QOL (EQ-5D-5L)

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Inclusion Criteria

- Confirmed diagnosis of MND (including subtypes)
- Over 18
- Women of childbearing age with a -ve pregnancy test
- Women of childbearing age and fertile men must be willing to use appropriate contraception
- Willing to comply with trial protocol and able to understand and complete questionnaires
- Written informed consent (In the case of limb dysfunction, verbal consent can be given in the presence of a witness who can sign)

Exclusion criteria

- FTD or significant psychiatric disorder that prevents informed consent being given
- Patients in a manic phase of bipolar
- Alcoholism (Self-reported)
- Active suicidal ideation (CSSRS)
- On concurrent investigational drug
- Known sensitivity to fructose – including hereditary intolerance
- Pregnancy or breastfeeding
- Abnormal blood results at screening

Exclusion criteria cont …/…

- If corrected QT interval on ECG is >450ms (>500ms in new protocol)
- Patient diagnosed with ventricular arrhythmias, significant heart block (PI discretion) or <6 weeks post MI
- Active Epilepsy
- History of proven peptic ulcer confirmed on endoscopy
- Already taking one of the IMPs
- Taking any of the following medications: Dextramethorphan, Amantadine, Ketamine, Monoamine oxidase inhibitors (MAOIs), Rasagiline, Selegiline, Safinamide, Tranylcyromine, Phenelzine, Isocarboxazid, Moclobemide
- Patients who the PI considers will not be able to comply with protocol

Visit Schedule

- Screening and baseline – face to face (Can be done as one appointment)
- Telephone calls weekly after starting drug to titration
- Telephone calls every 2 months to assess function (ALSFRS), AEs and resupply of IMP
- Face to face appointments at 6-12-18 months. May be done remotely if patient is to unwell to attend

Dosing

To reduce adverse reactions there is a dose titration at the start of treatment and the option for participants to remain on maximum tolerated dose:

- Week 1 - 2.5 mls
- Week 2 – 5 mls
- Week 3 - 7.5 mls
- Week 4 – 10 mls

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MND SMART Sub study

Aim:

To find out why people have taken part and why they withdraw from the study.

To understand how support of caregivers affects likelihood of people with MND to take part in MND SMART.

Outcome:

To guide how clinical trials are designed in the future, ensuring they meet the needs and expectations of pwMND.

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South Wales MND SMART

Patients can register via the MND SMART web page (MND-SMART.org)

- Since January 2020, 106 pwMND from Wales have registered.
- Screened at Research clinic 44 patients
- 33 randomised patients
- 11 Screen failures
- 20 on drug
- 11 withdrawals due to AEs/ PI discretion
- 7 observation arm
- 2 deaths

AEs

- Tiredness
- Light-headedness
- Headache
- Nausea
- Muscle ache
- Dry mouth
- Worsening of MND symptoms

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Participation in the trial

- Multiple questionnaires every 2 months for participant and carer for SMART and Sub Study
- Daily diary to record AEs and dosing
- Participant ID card
- GP informed via letter with trial information sheet that their patient is on the clinical trial
- Patient care updated with patients on trial

End of life

- Participants can stop IMP abruptly or have a rapid dose de-escalation at PI discretion as part of end of life care
- Appointments either completed remotely with assistance of the patient's carer/relative or not at all

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How to participate

- Register interest | MND-SMART
- Clinician referrals

Any Questions?