MS-SMART TRIAL
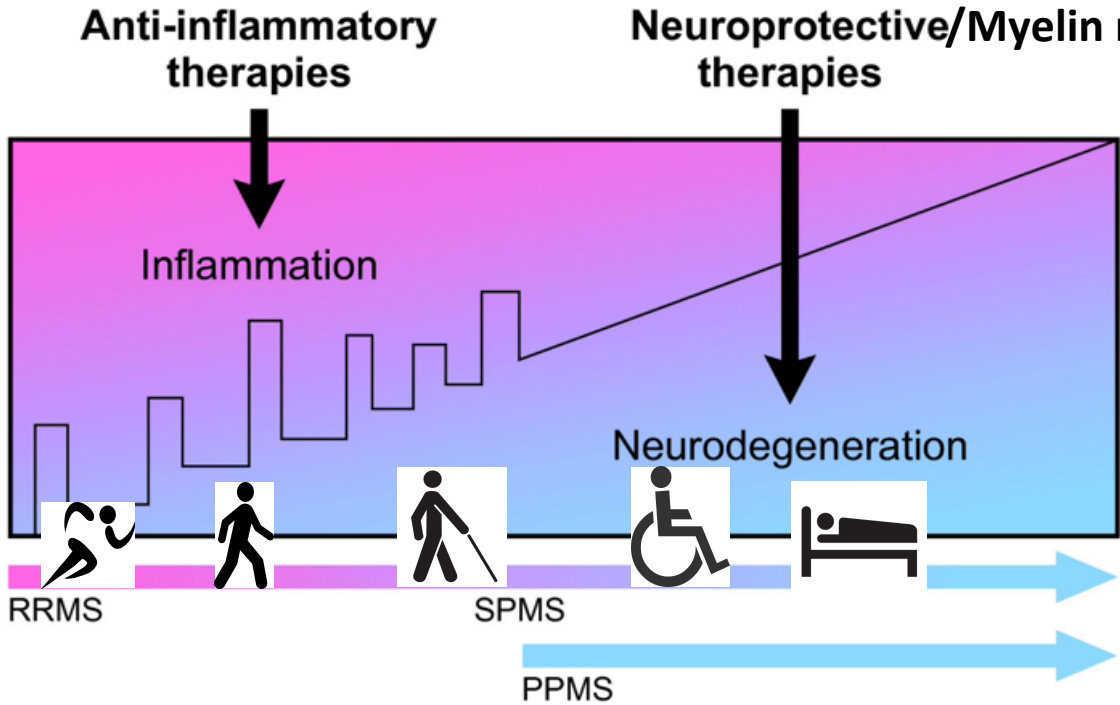
<u>M</u>ultiple <u>S</u>clerosis-<u>S</u>econdary Progressive <u>M</u>ulti-<u>A</u>rm <u>R</u>andomisation <u>T</u>rial.

The first multi-arm phase 2b randomised, double blind, placebo-controlled clinical trial comparing the efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis.
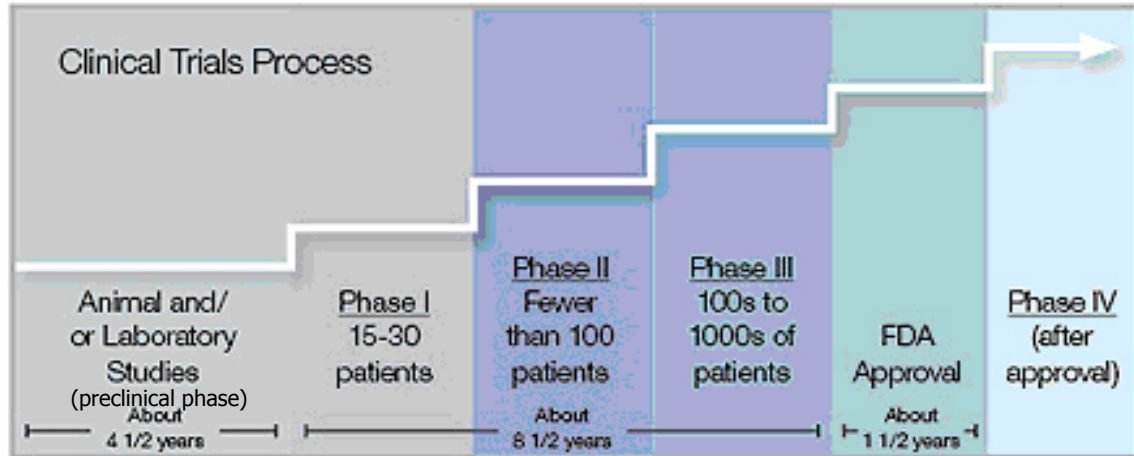
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UCL Institute of Neurology

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DRUG DEVELOPMENT: A LONG JOURNEY!

Clinical Trials Process

Animal and/ or Laboratory Studies (preclinical phase) About 4 1/2 years	Phase I 15-30 patients	Phase II Fewer than 100 patients	Phase III 100s to 1000s of patients	FDA Approval	Phase IV (after approval)

About 8 1/2 years — About 1 1/2 years

Animal/laboratory: first evidence of efficacy and accumulation of evidence.
Phase I: small number of patients to test safety
Phase II: larger number of patients to test efficacy (it allows to identify the markers of efficacy of a drug)
Phase III: very large number of patients to confirm efficacy and compare the study drug with the standard one.
Phase IV: post marketing.

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MS SMART

NEW CLINICAL TRIAL DESIGN

- Parallel multi arm design
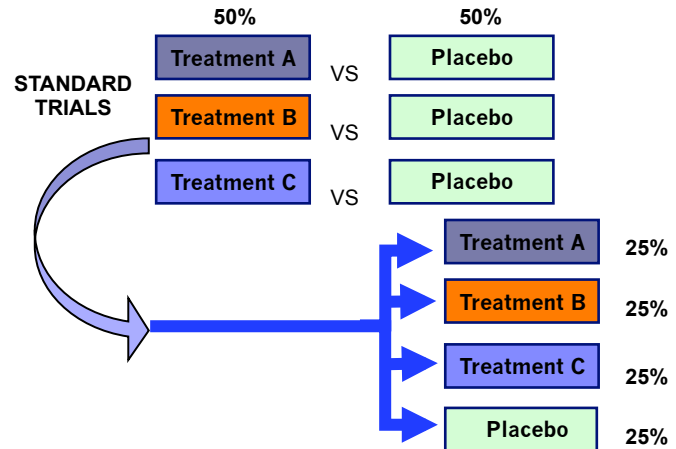
(4 arms, 3 active and 1 placebo)

DRUG REPURPOSING

- Fluoxetine
- Amiloride
- Riluzole

Phase 2 trial (proof of concept)

- Primary objective: to slow-down disability progression using putative neuroprotective drugs in SPMS

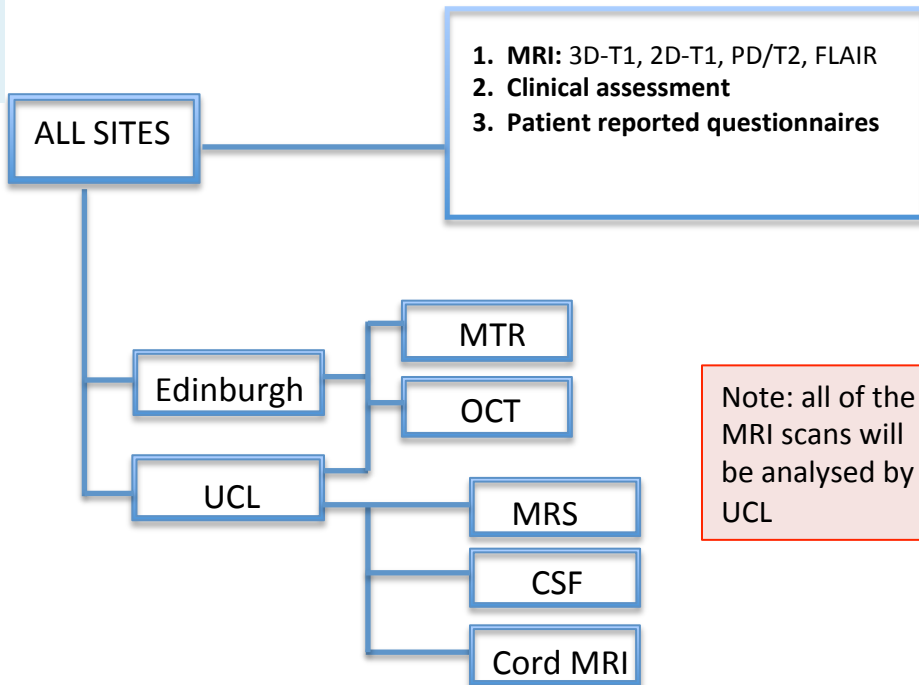*- Primary outcome:* MRI-derived percentage of brain volume change after 96 weeks.

SITES INVOLVED AND TEST DONE

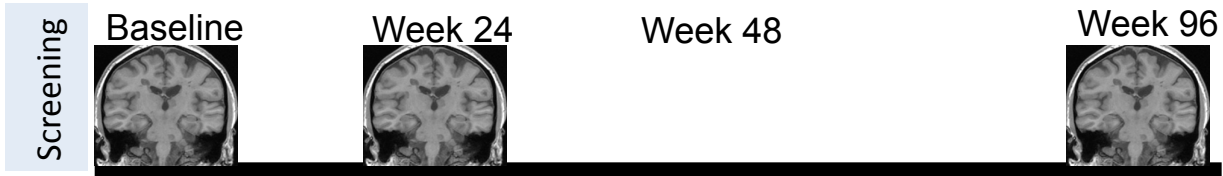Multi-centre study (13 sites in the UK)

Optional Sub-studies are carried out in 2 of these sites
- Advanced MRI
  - Spinal Cord (SC)
  - Proton (1H) MR spectroscopy (MRS)
  - Brain magnetization transfer ratio (MTR)
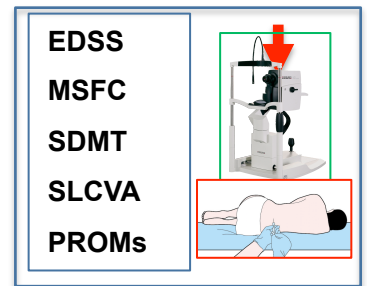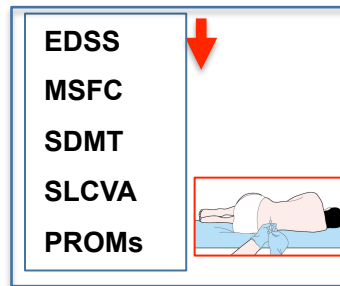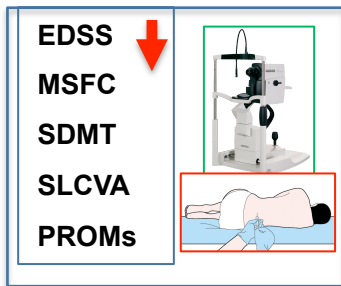- OCT
- CSF

ALL SITES

1. **MRI:** 3D-T1, 2D-T1, PD/T2, FLAIR
2. **Clinical assessment**
3. **Patient reported questionnaires**

Edinburgh — MTR, OCT

UCL — MRS, CSF, Cord MRI

Note: all of the MRI scans will be analysed by UCL

To establish whether any of the 3 selected drugs slowed the rate of brain volume loss in SPMS over 96 weeks using MRI-derived PBVC [calculated with SIENA].

Brain extraction is automatically obtained using the GIF algorithm

Baseline brain   Registration of whole repeat brain to whole baseline brain   Repeat brain

Volume of change quantified
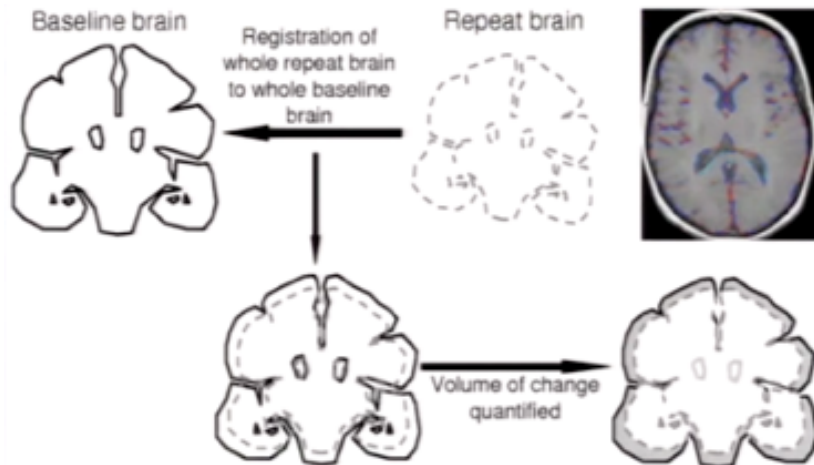
Cross-sectional analysis is currently ongoing: normalized brain volume

FLAIR PD 3DT1

Lesion filling

Brain extraction & registration to the MNI template
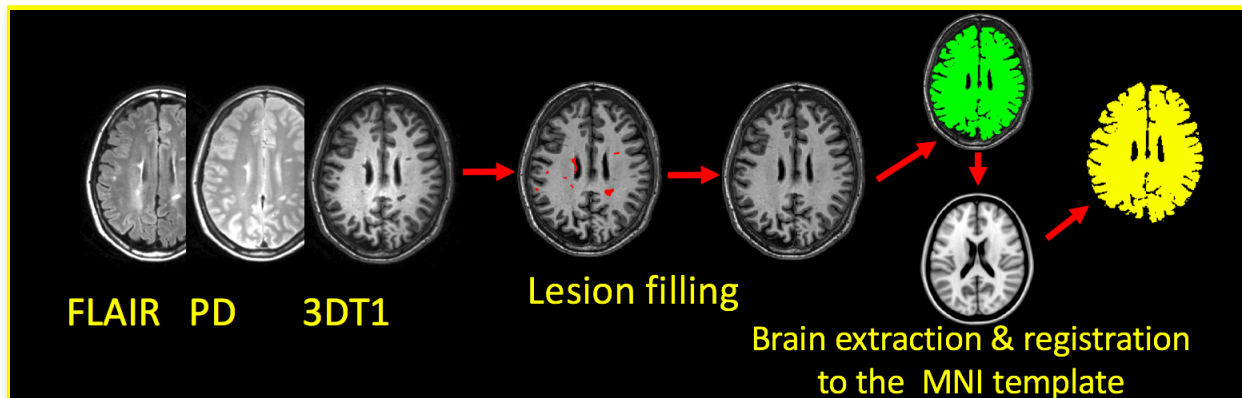
Lesions were contoured on the PD scans based on hyperintensity in the PD/T2 and FLAIR scans using a semi-automatic method (Jim 7 Software, Xinapse Systems, UK). The lesion mask was then used to fill the lesion on the 3DT1-weighed image. Brain was then segmented automatically using the GIF algorithm the brain mask was then registered to the MNI template to obtain final normalised brain volume. PD= proton density. FLAIR: Fluid attenuated inversion recovery. GIF= geodesic information flows.

MRI: advanced protocol

Brain magnetisation transfer ratio (MTR)

Indirect measure of demyelination and remyelination (MTR increase may reflect remyelination). The measurement of grey matter MTR is used to infer cortical demyelination and predict potential neuroprotection.

Proton (1H) MR spectroscopy (MRS)

Detects metabolites in the brain, reflecting neurodegenerative processes. Glutamate, N-Acetyl Aspartate (NAA), and Myoinositol will be measured. Particular focus is on glial cell proliferation and activation, which are prominent features of SPMS and potentially contribute to on-going neurodegeneration.

Cervical cord cross-sectional area

This is a measure of cord atrophy, which correlates to locomotor disability. Cervical cord phase sensitive inversion recovery (PSIR) will be acquired from C2-C4. The active surface modelling to outline the spinal cord will be applied.

Why so much attention on spinal cord?

- Cord atrophy correlates with locomotor disability in MS
- Some studies have shown high sensitivity of this measure to disability progression.
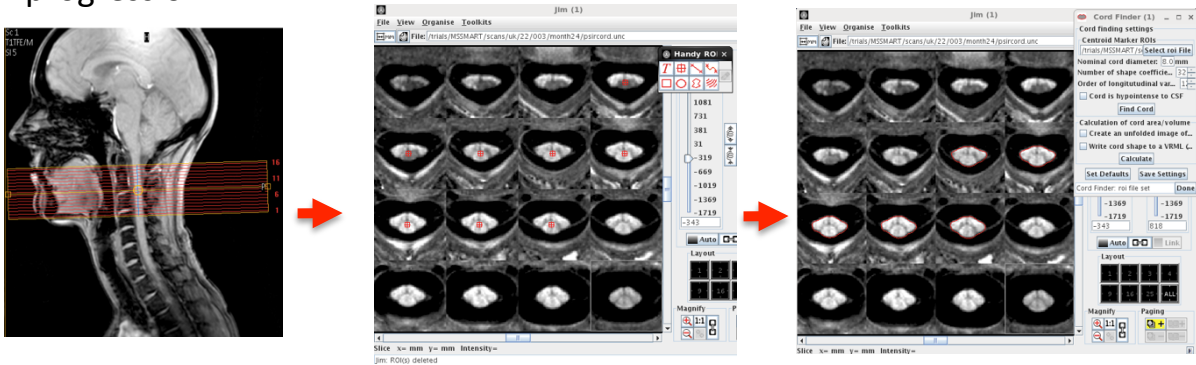
16 axial scans from a high resolution 3D-PSIR sequence (0.5x0.5x3) are acquired from C2-C3 (where the center of the acquisition volume is positioned). MUCCA is calculated using a semi-automated software Jim7, Xinapse Systems, UK. Firstly, a marker is manually positioned in the center of the 5 slices between C2-C3 (slices 7-11). Subsequently, Jim7 automatically finds the cord area of the 5 slices, that are finally averaged to get MUCCA. PSIR= Phase Inversion Recovery. MUCCA= mean upper cervical cord cross-sectional area.

Cawley et al, MSJ 2017
Kearney H et al, Nat Rev Neurol. 2015
Kearny at al, JMRI, 2014

- Cross-sectional often semi-automated way

- Imaging registration difficult

- Positioning of the neck/head may affect cross-sectional area measures

- Cord lesions creates artefacts
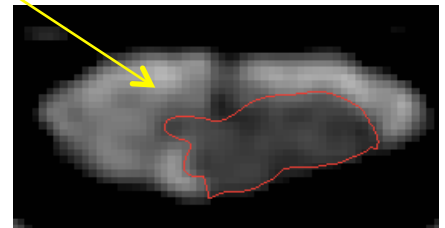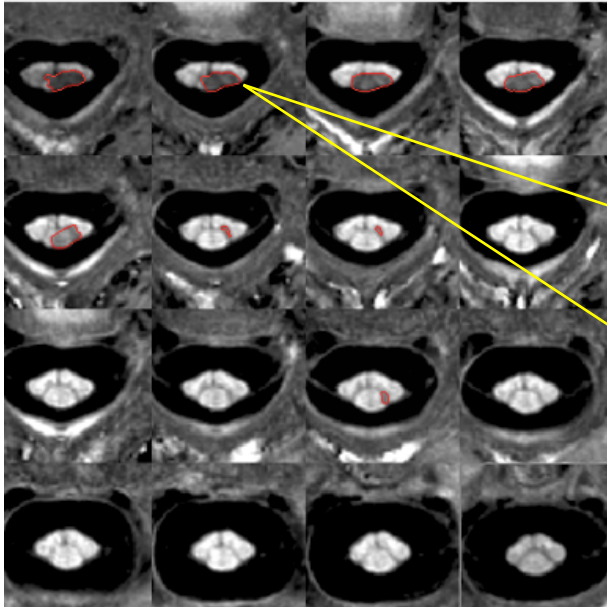
ADDITIONAL ANALYSIS: UPPER CORD LESIONS

… work in progress

UCL

- Trial is ongoing: 445 patients recruited

- Advanced MRI for sub-studies collected:
- MTR:137
- Cervical cord: 145
- MRS: 145

- MRI and other longitudinal analyses are ongoing…

- Last trial visit will occur in April 2018 and primary outcome results announced at ECTRIMS 2018