SUPPLEMENTARY MATERIAL

Table I. Other imaging marker at baseline and 2 years in the two treatment groups- intention-to-treat analysis

MRI parameter	Raw, Mean (SD)				Change Mean (SD) (%)	
	Standard		Intensive		Standard	Intensive
	Baseline	24 months	Baseline	24 months	Baseline – 24 months	Baseline – 24 months
DTI-FA peak height (mm²/s)	3.22×10^3 (2.31×10^{-4})	3.18×10^{-3} (2.82×10^{-4})	3.22×10^{-3} (2.47×10^{-4})	3.19×10^{-3} (2.33×10^{-4})	-0.04×10^{-3} (1.60×10^{-4}) (-1.2)	-0.03×10^{-3} (1.93×10^{-4}) (-0.9)
DTI – MD peak location (mm²/s)	7.65×10^{-4} (4.80×10^{-5})	7.69×10^{-4} (4.46×10^{-5})	7.62×10^{-4} (3.42×10^{-5})	7.66×10^{-4} (3.83×10^{-5})	0.04×10^{-4} (0.22×10^{-4}) (0.5)	0.04×10^{-4} (0.25×10^{-4}) (0.5)
DTI – FA peak location (mm²/s)	3.10×10^{-1} (4.75×10^{-2})	3.04×10^{-1} (4.84×10^{-2})	3.10×10^{-1} (4.98×10^{-2})	3.08×10^{-1} (3.99×10^{-2})	-0.06×10^{-1} (0.3×10^{-1}) (-1.9)	-0.02×10^{-1} (0.5×10^{-1}) (-0.7)
DTI- MD median (mm²/s)	7.86×10^{-4} (4.86×10^{-5})	7.95×10^{-4} (5.31×10^{-5})	7.90×10^{-4} (4.42×10^{-5})	7.97×10^{-4} (4.60×10^{-5})	0.10×10^{-4} (0.16×10^{-4}) (1.3)	0.07×10^{-4} (0.18×10^{-4}) (0.9)
DTI - FA median (mm²/s)	3.35×10^{-1} (2.87×10^{-2})	3.30×10^{-1} (3.13×10^{-2})	3.33×10^{-1} (2.78×10^{-2})	3.31×10^{-1} (2.78×10^{-2})	-0.06×10^{-1} (0.14×10^{-1}) (-1.8)	-0.02×10^{-1} (0.12×10^{-2}) (-0.6)

MRI parameter	Adjusted, Mean (SE) (95% CI) at 24 months[‡]		p-value
	Standard	Intensive	
DTI-FA peak height (mm²/s)	3.17×10^{-3} (2.61×10^{-5}) $(3.12 \times 10^{-3} - 3.23 \times 10^{-3})$	3.19×10^{-3} (2.51×10^{-5}) $(3.15 \times 10^{-3} - 3.25 \times 10^{-3})$	0.57^*
DTI – MD peak location (mm²/s)	7.68×10^{-4} (3.44×10^{-6}) $(7.61 \times 10^{-4} - 7.75 \times 10^{-4})$	7.66×10^{-4} (3.31×10^{-6}) $(7.60 \times 10^{-4} - 7.73 \times 10^{-4})$	0.71^*
DTI – FA peak location (mm²/s)	3.05×10^{-1} (5.39×10^{-3}) $(2.94 \times 10^{-1} - 3.16 \times 10^{-1})$	3.08×10^{-1} (5.19×10^{-3}) $(2.98 \times 10^{-1} - 3.18 \times 10^{-1})$	0.69^*
DT I- MD median (mm²/s)	7.97×10^{-4} (2.77×10^{-6}) $(7.91 \times 10^{-4} - 8.03 \times 10^{-4})$	7.95×10^{-4} (2.66×10^{-6}) $(7.90 \times 10^{-4} - 8.01 \times 10^{-4})$	0.58^*
DTI - FA median (mm²/s)	3.29×10^{-1} (1.91×10^{-3}) $(3.25 \times 10^{-1} - 3.33 \times 10^{-1})$	3.32×10^{-1} (1.84×10^{-3}) $(3.28 \times 10^{-1} - 3.36 \times 10^{-1})$	0.23^*

DTI= Diffusion Tensor Imaging; FA= fractional anisotropy; MD= mean diffusivity, %= percentage change

[*]Analysis of covariance was employed to test whether there is a difference between treatment groups for any DTI marker at 24 months while accounting for the marker's baseline measure and study site.

[‡] Means, standard errors and 95% confidence intervals adjusted by the baseline measure and study site
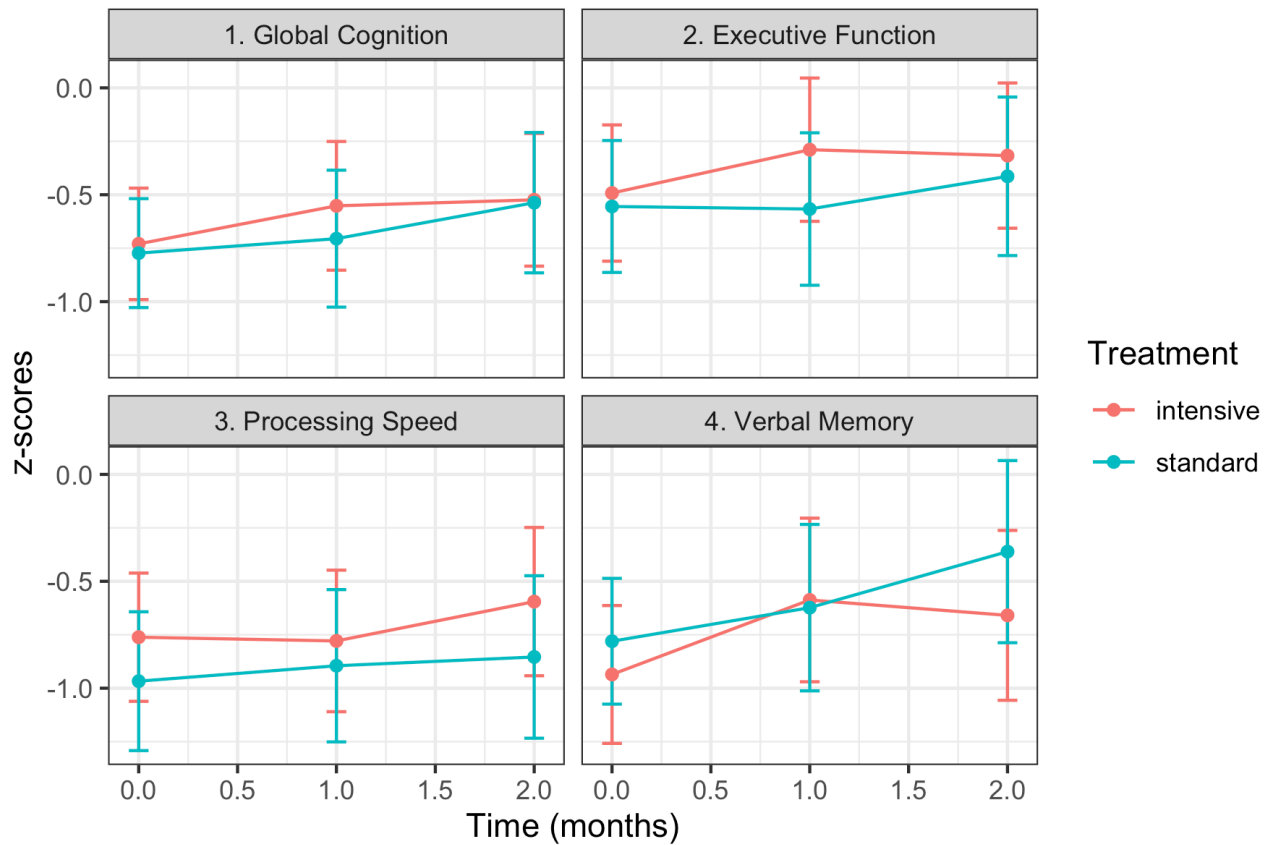
Figure I. Cognition in the two treatment arms - intention to treat analysis. Cognition in the two treatment arms- per-protocol analysis. The means and 95% confidence intervals in each treatment group are shown per time point for each normalised cognitive index score. Testing whether the change in cognition depends on treatment groups, a linear mixed model with a fixed effect interaction visit x treatment and patients as a random intercept was employed. Change in cognition did not depend on the treatment group for Global Cognition ($F_{(2, 196.64)}$= 0.42, p= 0.66), Executive Function ($F_{(2, 197.04)}$= 1.01, p= 0.37), processing speed ($F_{(2, 196.69)}$= 0.55, p= 0.58) or verbal memory ($F_{(2, 195.37)}$= 1.12, p= 0.33).
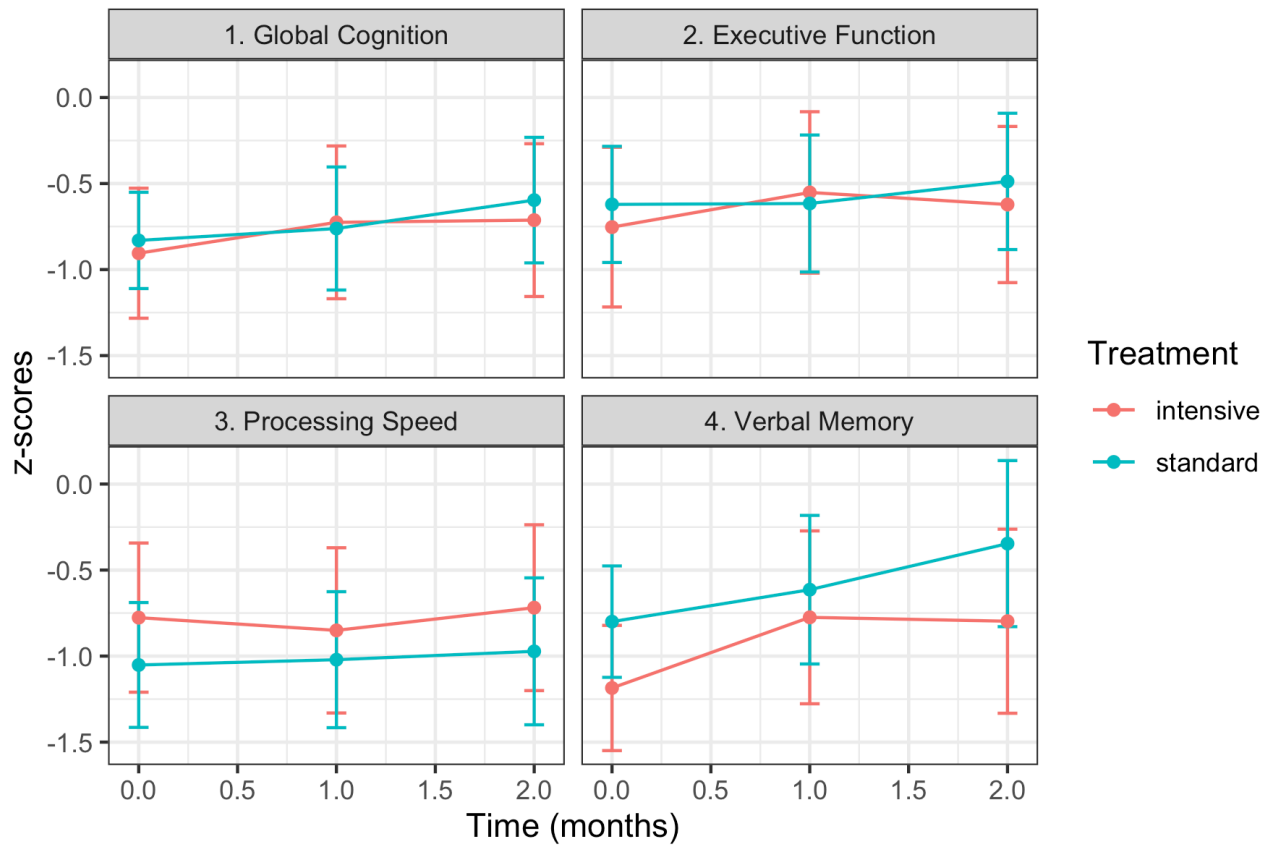
Figure II: Cognition in the two treatment arms- per-protocol analysis. The means and 95% confidence intervals in each treatment group are shown per time point for each normalised cognitive index score. Testing whether the change in cognition depends on treatment groups, a linear mixed model with a fixed effect interaction visit x treatment and patients as a random intercept was employed. Change in cognition did not depend on the treatment group for global cognition ($F_{(2, 142.85)}$= 0.12, p= 0.89), executive function ($F_{(2, 143.29)}$= 0.33, p= 0.72), processing speed ($F_{(2, 142.42)}$= 0.21, p= 0.81) or verbal memory ($F_{(2, 141.33)}$= 0.62, p= 0.54).

Table II. Other imaging marker at baseline and 2 years in the two treatment groups- per-protocol analysis

MRI parameter	Raw, Mean (SD)				Change Mean (SD) (%)	
	Standard		Intensive		Standard	Intensive
	Baseline	24 months	Baseline	24 months	Baseline – 24 months	Baseline – 24 months
DTI – FA peak height (mm²/s)	3.26×10^{-3} (2.13×10^{-4})	3.23×10^{-3} (2.73×10^{-4})	3.22×10^{-3} (2.41×10^{-4})	3.17×10^{-3} (2.45×10^{-4})	-3.11×10^{-5} (1.72×10^{-4}) (-1.0)	-4.77×10^{-5} (2.20×10^{-4}) (-1.5)
DTI – MD peak location (mm²/s)	7.73×10^{-4} (4.49×10^{-5})	7.75×10^{-4} (4.39×10^{-5})	7.60×10^{-4} (3.28×10^{-5})	7.64×10^{-4} (3.63×10^{-5})	2.06×10^{-6} (2.24×10^{-5}) (0.3)	4.46×10^{-6} (2.70×10^{-5}) (0.6)
DTI – FA peak location (mm²/s)	3.04×10^{-1} (4.26×10^{-2})	2.98×10^{-1} (4.56×10^{-2})	3.08×10^{-1} (5.27×10^{-2})	3.12×10^{-1} (3.91×10^{-2})	-0.06×10^{-1} (0.34×10^{-1}) (2.0)	0.04×10^{-1} (0.53×10^{-1}) (1.3)
DT I- MD median (mm²/s)	7.93×10^{-4} (4.59×10^{-5})	8.03×10^{-4} (5.19×10^{-5})	7.89×10^{-4} (3.92×10^{-5})	7.95×10^{-4} (4.17×10^{-5})	9.76×10^{-6} (1.66×10^{-5}) (1.2)	6.04×10^{-6} (2.11×10^{-5}) (0.8)
DTI - FA median (mm²/s)	3.32×10^{-1} (2.73×10^{-2})	3.25×10^{-1} (3.02×10^{-2})	3.32×10^{-1} (2.91×10^{-2})	3.32×10^{-1} (2.84×10^{-2})	-0.07×10^{-1} (0.14×10^{-1}) (2.1)	-3.96×10^{-4} (0.12×10^{-1}) (-0.1)

MRI parameter	Adjusted, Mean (SE) (95% CI) at 24 months[‡]		p-value
	Standard	Intensive	
DTI – FA peak height (mm²/s)	3.21×10^{-3} (3.03×10^{-5}) $(3.15 \times 10^{-3} - 3.27 \times 10^{-3})$	3.20×10^{-3} (3.43×10^{-5}) $(3.13 \times 10^{-3} - 3.27 \times 10^{-3})$	0.93^{*}
DTI – MD peak location (mm²/s)	7.71×10^{-4} (4.06×10^{-6}) $(7.63 \times 10^{-4} - 7.78 \times 10^{-4})$	7.69×10^{-4} (4.60×10^{-6}) $(7.60 \times 10^{-4} - 7.78 \times 10^{-4})$	0.78^{*}
DTI – FA peak location (mm²/s)	3.00×10^{-1} (6.51×10^{-3}) $(2.87 \times 10^{-1} - 3.13 \times 10^{-1})$	3.09×10^{-1} (7.36×10^{-3}) $(2.94 \times 10^{-1} - 3.24 \times 10^{-1})$	0.38^{*}
DTI- MD median (mm²/s)	8.01×10^{-4} (3.33×10^{-6}) $(7.94 \times 10^{-4} - 8.08 \times 10^{-4})$	7.98×10^{-4} (3.76×10^{-6}) $(7.90 \times 10^{-4} - 8.05 \times 10^{-4})$	0.56^{*}
DTI - FA median (mm²/s)	3.26×10^{-1} (2.21×10^{-3}) $(3.21 \times 10^{-1} - 3.30 \times 10^{-1})$	3.31×10^{-1} (2.50×10^{-3}) $(3.26 \times 10^{-1} - 3.36 \times 10 \text{-}1)$	0.14^{*}

DTI= Diffusion Tensor Imaging; FA= fractional anisotropy; MD= mean diffusivity, %= percentage change

*Analysis of covariance was employed to test whether there is a difference between treatment groups for any DTI marker at 24 months while accounting for the marker's baseline measure and study site.

[‡] Means, standard errors and 95% confidence intervals adjusted by the baseline measure and study site

Table III. Change in cognitive and MRI measures over the 2 years follow-up period in the whole population. *Interquartile range additionally computed for count data

MRI parameter	Raw Mean (SD, IQR*)			Change Raw Mean, (SD, IQR*) (%)	p-value
	Baseline	12 months	24 months	2 years	
DTI-MD peak height (mm^2/s)	13.3×10^{-3} (2.4×10^{-3})	--	12.5×10^{-3} (2.3×10^{-3})	-0.8×10^{-3} (1.2×10^{-3}) (-6.0)	3.39×10^{-8}
NBV (whole brain, ml)	1353.8 (112.6)	--	1322.6 (117.7)	-31.3 (30.3) (-2.3)	9.09×10^{-16}
WMH lesion volume (% brain) (log10)	3.4 (2.2)	--	3.8 (2.5)	0.4 (0.8) (11.8)	9.30×10^{-6}
Lacunes (count)	4.3 (4.7, 5.0)	--	6.2 (5.9, 7.5)	1.9 (3.1, 3.0) (44.2)	9.28×10^{-8}
Cerebral microbleeds (count)	4.0 (7.5, 6.25)	--	4.5 (8.4, 5.0)	0.5 (1.9, 1.0) (12.5)	0.01
Cognition	**Estimated Mean (SE)**			**Change Estimated Mean (SE) (%)**	**p-value**
	Baseline	12 months	24 months	2 years	
Global Cognition	-0.75 (0.10)	-0.61 (0.10)	-0.56 (0.10)	0.20 (0.07) (26.7)	0.01
Executive Function	-0.52 (0.12)	-0.43 (0.12)	-0.40 (0.12)	0.13 (0.09) (25.0)	0.31
Processing Speed	-0.87 (0.12)	-0.84 (0.12)	-0.76 (0.12)	0.11 (0.08) (12.6)	0.37
Verbal Memory	-0.85 (0.12)	-0.59 (0.13)	-0.50 (0.13)	0.35 (0.10) (41.2)	0.002

Table IV. Cognition over time with missing values mean imputed. Missing cognitive scores were imputed using the scores' mean at the respective time point. The mean and standard deviation at each time point is shown. It was tested whether there was a significant change over time. The results are similar to those used in the main in which missing cognitive scores were removed from the analysis.

Cognitive Index	TP	Mean (SD)	Significance
Global Cognition	Baseline	-0.743 (0.931)	$F(2, 220)= 5.63$, $p= 0.004143$
	12 months	-0.609 (1.032)	
	24 months	-0.523 (1.024)	
Executive function	Baseline	-0.524 (1.139)	$F(2, 220)= 1.16$ $p= 0.3159$
	12 months	-0.428 (1.179)	
	24 months	-0.345 (1.116)	
Processing speed	Baseline	-0.839 (1.119)	$F(2, 220)= 2.09$, $p= 0.1262$
	12 months	-0.829 (1.144)	
	24 months	-0.727 (1.187)	
Verbal memory	Baseline	-0.873 (1.093)	$F(2, 220)= 6.60$, $p= 0.001646$
	12 months	-0.617 (1.247)	
	24 months	-0.523 (1.301)	

Table V. Cognition over time with missing values imputed by regression approach. Missing cognitive scores were imputed using a regression approach. Missing values at the follow-up time points were predicted based on non-missing cognitive score(s) at previous time points. The mean and standard deviation at each time point is shown. It was tested whether there was a significant change over time. The results are similar to those used in the main in which missing cognitive scores were removed from the analysis.

Cognitive Index	TP	Mean (SD)	Significance
Global Cognition	Baseline	-0.743 (0.944)	$F(2, 214)= 5.23$, $p= 0.006071$
	12 months	-0.607 (1.087)	
	24 months	-0.553 (1.098)	
Executive function	Baseline	-0.524 (1.149)	$F(2, 216)= 1.41$, $p= 0.2456$
	12 months	-0.433 (1.218)	
	24 months	-0.392 (1.195)	
Processing speed	Baseline	-0.839 (1.140)	$F(2, 214.17)= 0.90$ $p= 0.4074$
	12 months	-0.844 (1.192)	
	24 months	-0.759 (1.256)	
Verbal memory	Baseline	-0.873 (1.119)	$F(2, 212.3)= 7.30$, $p= 0.0008622$
	12 months	-0.585 (1.333)	
	24 months	-0.509 (1.372)	

Table VI. List of the reported side effects

SE effects	Intensive Treatment	Standard Treatment
Aching in muscles	0	1
Acute kidney injury	1	0
Altered sensation to thumb and lip	0	1
Ankle oedema	3	7
Bladder weakness	0	1
Breathlessness	2	1
Bruised big toe nail	0	1
Carpal Tunnel syndrome	0	1
Clumsiness	0	1
Collapse	0	2
Cough	0	1
Diagnosed with type 2 diabetes	0	1
Diarrhoea	1	3
Difficulty getting to sleep	0	1
Difficulty swallowing	1	0
Drowsiness	1	0
Emotional, depressed mood	0	1
Epistaxis	1	0
Erectile dysfunction	0	2
Fainting spell	1	0
Fatigue	1	0
Feeling cold	0	1
Feeling extremely tired	1	0
Feet swelling	0	1
Fibula and rib fracture	0	1
Frozen shoulder	0	1
Gait apraxia secondary to small vessel disease	0	1
Gastroenteritis	1	0
Hand numbness	0	1
Headache	0	6
Heartburn	1	0
Hernia in groin	1	0
Hip pain, due to osteoarthritis	0	1
Hyperkalemia & Hyponatremia	0	1
Hypoglycemia	1	0
Impotence	1	1
Incontinence	0	1
Indigestion	0	2
Infection in Sinus	0	1

Iron Deficiency	0	1
Leg cramps	0	2
Leg swelling	1	1
Liver disease	0	1
Loss of sense of taste and smell	0	1
Memory troubles	1	0
Migraine	0	2
Migraine with Aura.	0	1
Nausea	0	3
Night sweats	0	1
Non-postural fall	0	1
Numbness in fingers when arms elevated	0	1
Numbness in leg	0	1
Ongoing mood and memory troubles	0	1
Pain in back and legs	1	0
Pain in both ankles	0	1
Pedal oedema	0	2
Protein in urine	0	1
Rectal Bleeding	0	1
Red lesion on forehead	0	1
Reduced sensation to arm and face	0	1
Re-occurrence of central serous retinopathy	0	1
Severe vomiting	1	0
Shoulder/chest numbness	1	0
Skin rash	1	0
Sleepiness	0	1
Slight ankle swelling	1	0
Slurred speech	0	1
Some bruising on minimal trauma	0	1
Sore throat	0	1
Sporadic periods of sensory deficit in shoulder	1	0
Student's elbow	1	0
Swelling of calves and ankles	1	0
Swelling right foot at night	0	1
Swollen calves	1	0
Tear duct enlargement	0	1
Tiredness	0	2
Tooth Infection	0	1
Trigeminal neuralgia	1	0
Urinary Tract Infection	2	1

Unsteady gait	1	0
Vertigo	2	0
Vitamin D deficiency	1	0
Vomiting	1	0
Woke up with room swimming and felt clammy	1	0
Worsening memory	0	1