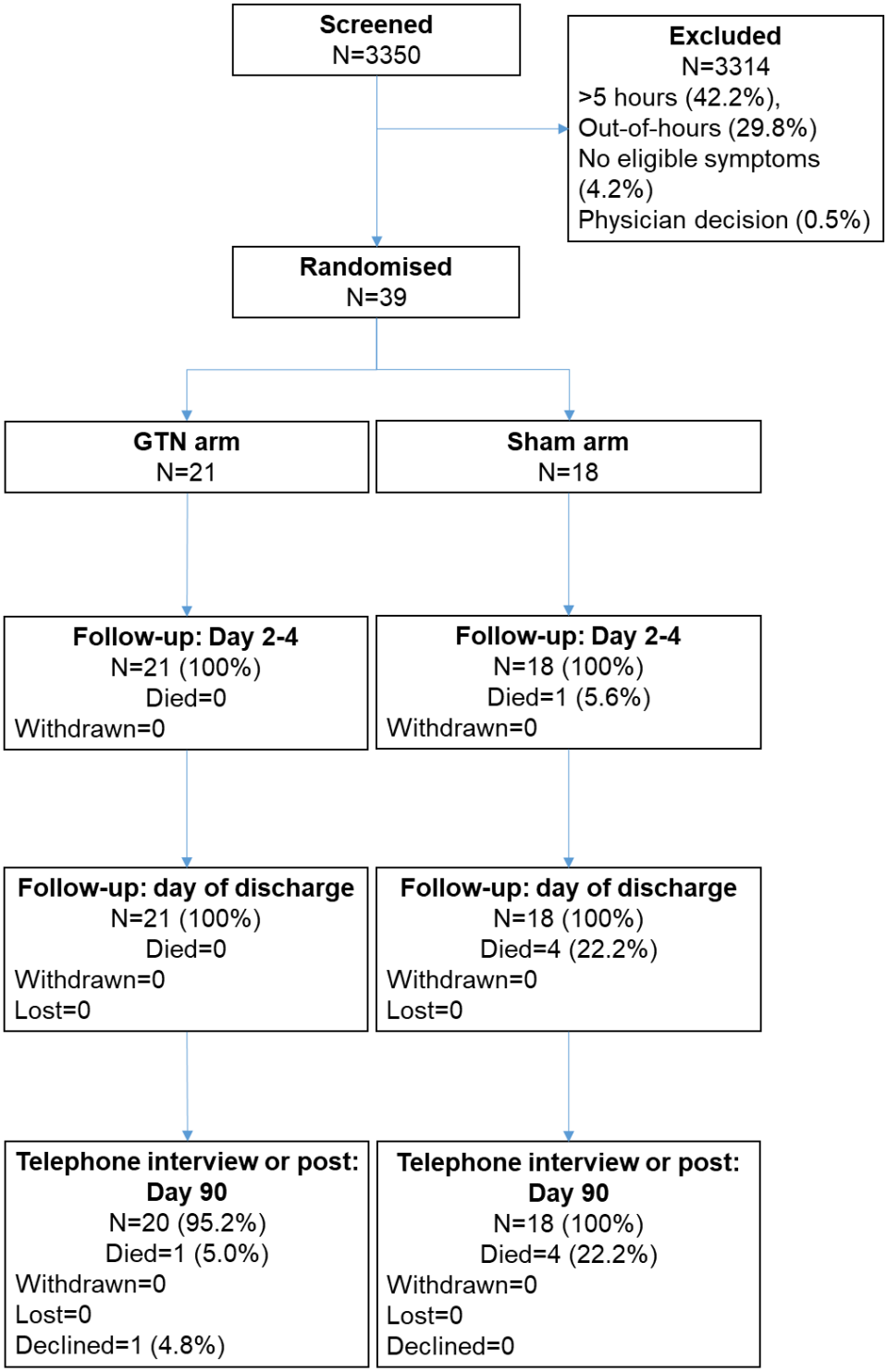
ENOS-2 Results summary

CONSORT diagram, enrolment and follow-up.



GTN: glyceryl trinitrate. Data are number (%).

Baseline characteristics

Data are number (%), median [interquartile range] or mean (standard deviation).

Characteristic	N	All	GTN	Sham
Number of patients		39	21	18
Age (years) †	39	72.3 (13.2)	71.0 (11.5)	73.7 (15.1)
Sex, female (%)	39	16 (41.0)	9 (42.9)	7 (39.9)
Ethnicity				
Asian	39	2 (5.1)	2 (9.5)	0 (0.0)
White	39	37 (94.9)	19 (90.5)	18 (100.0)
Time to randomisation (min) †	39	216 [186, 251]	218 [192, 264]	196 [186, 245]
<4 hours/240 minutes (%)	39	27 (69.2)	14 (66.7)	13 (72.2)
Candidate for reperfusion †	39	22 (56.4)	11 (52.4)	11 (61.1)
Pre-morbid mRS >0 (%)	39	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	1.0 [0.0, 1.0]
Medical history (%)				
Treated hypertension	39	24 (61.5)	11 (52.4)	13 (72.2)
ACE-Inhibitor	39	13 (33.3)	4 (19.0)	9 (50.0)
Angiotensin-II receptor antagonist	39	5 (12.8)	3 (14.3)	2 (11.1)
Alpha-blocker	39	2 (5.1)	1 (4.8)	1 (5.6)
Beta Blocker	39	8 (20.5)	4 (19.0)	4 (22.2)
Calcium channel blocker	39	9 (23.1)	4 (19.0)	5 (27.8)
Centrally acting agent	39	0 (0.0)	0 (0.0)	0 (0.0)
Diuretic	39	4 (10.3)	2 (9.5)	2 (11.1)
Labetalol	39	0 (0.0)	0 (0.0)	0 (0.0)
Renin	39	1 (2.6)	0 (0.0)	1 (5.6)
Other antihypertensives	39	2 (5.1)	1 (4.8)	1 (5.6)
Stroke	39	10 (25.6)	5 (23.8)	5 (27.8)
Transient ischaemic attack	38	7 (18.4)	3 (15.0)	4 (22.2)
Ischaemic heart disease	39	8 (20.5)	4 (19.0)	4 (22.2)
Diabetes mellitus	39	9 (23.1)	6 (28.6)	3 (16.7)
Hyperlipidaemia	39	15 (38.5)	8 (38.1)	7 (38.9)
Smoking, current (%)	37	9 (24.3)	7 (33.3)	2 (11.1)
Alcohol >21 units per week	36	3 (7.7)	2 (9.5)	1 (5.6)
AF, current/previous	39	7 (17.9)	4 (19.0)	3 (16.7)

COVID-19, definite/possible	39	3 (7.7)	2 (9.5)	1 (5.6)
Nitrate use before stroke	39	2 (5.1)	2 (9.5)	0 (0.0)
Side of lesion, right (%)	32	18 (56.3)	8 (44.4)	10 (71.4)
NIHSS (/42) †	39	9.1 (6.3)	7.6 (4.2)	10.9 (7.9)
GCS <15 (%)	39	11 (28.2)	5 (23.8)	6 (33.3)
OCSP classification (%)				
Total anterior	39	11 (28.2)	5 (23.8)	6 (33.3)
Partial anterior	39	18 (46.2)	9 (42.9)	9 (50.0)
Lacunar	39	10 (25.6)	7 (33.3)	3 (16.7)
Posterior	39	0 (0.0)	0 (0.0)	0 (0.0)
Qualifying event Σ				
Ischaemic stroke (%) ‡	39	33 (84.6)	19 (90.5)	14 (77.8)
Cardioembolic	33	12 (36.4)	7 (36.8)	5 (35.7)
Large vessel	33	8 (24.2)	3 (15.8)	5 (35.7)
Small vessel	33	6 (18.2)	4 (21.1)	2 (14.3)
Other	33	9 (27.3)	6 (31.6)	3 (21.4)
Not determined	33	1 (3.0)	0 (0.0)	1 (7.1)
Primary intracerebral haemorrhage	39	1 (2.6)	1 (4.8)	0 (0.0)
Transient ischaemic attack	39	4 (10.3)	1 (4.8)	3 (16.7)
Stroke mimic	39	1 (2.6)	0 (0.0)	1 (5.6) *ƒ*

AF: atrial fibrillation; BP: blood pressure; bpm: beats per minute; GCS: Glasgow Coma Scale; ICH: intracerebral haemorrhage; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; OCSP: Oxfordshire Community Stroke Project classification.

Data are number (%), median [interquartile range], or mean (standard deviation).

Percentages exclude missing values from denominators.

† Minimisation variable

‡ Stratification variable

ƒ Functional neurological disorder

¶ Sum may exceed 100% because of mixed aetiology.

Σ Qualifying event is determined by investigator by discharge.

Feasibility outcomes
Data are number (%).

Measure	Metric	Achieved (%)
Recruitment		
Overall		39/120 (32.5)
Target patients	100 with ischaemia 20 with ICH	37/100 (37.0) 1/20 (5.0)
Primary		
Retention of enrolees at Day 90 (follow-up)	>70/120 (58.3)	38/39 (97.4)
Treatment compliance/ adherence		
Received GTN/sham	All 2 days treatment	33/39 (84.6)
	First day treatment	37/39 (94.9)

Outcomes at days 2 and 90

Data are number of patients (%), median [interquartile range], or mean (standard deviation) score.

Outcome	N	All	GTN	Sham
Participants	39	39	21	18
Day 2 (or discharge)				
Death, all cause (%)	39	1 (2.6)	0 (0.0)	1 (5.6)
Clinical neurological deterioration (%)	39	2 (5.1)	0 (0.0)	2 (11.1)
Recurrent stroke (%) ‡	39	1 (2.6)	1 (4.8)	0 (0.0)
Symptomatic ICH (%) ‡	39	1 (2.6)	0 (0.0)	1 (5.6)
Clinical hypotension (%) ‡	39	8 (20.5)	4 (19.0)	4 (22.2)
Clinical hypertension (%) ‡	39	3 (7.7)	1 (4.8)	2 (11.1)
Headache (%) ‡	39	7 (17.9)	6 (28.6)	1 (5.6)
NIHSS (/43)	33	7.0 (10.1)	4.1 (4.2)	10.5 (13.7)
Dysphagia severity rating scale (/13)	39	2.4 (4.2)	2.0 (3.7)	3.0 (4.9)
Discharge data				
Hospital stay after randomisation (days)	39	13.4 (21.5)	17.3 (26.6)	8.8 (12.6)
Death or not discharged home (%)	39	7 (17.9)	2 (9.5)	5 (27.8)
Day 90				
modified Rankin Scale (/6)	38	2.9 (1.8)	2.8 (1.7)	3.0 (1.8)

Death (%)	39	5 (12.8)	1 (4.8)	4 (22.2)
Barthel Index (/100)	38	72.0 (38.8)	71.8 (35.8)	72.2 (43.0)
t-MMSE score (/22)	31	16.1 (7.8)	18.2 (5.7)	14.2 (9.2)
TICS-M score (/39)	31	20.2 (10.6)	24.3 (8.5)	16.3 (11.0)
Verbal fluency (animal naming)	32	14.9 (9.6)	18.1 (8.5)	12.1 (9.8)
EQ-5D-5L	38	0.5 (0.3)	0.5 (0.4)	0.5 (0.3)
EQ-visual analogue scale	37	56.6 (29.5)	62.2 (26.7)	50.8 (31.9)
Zung depression scale	32	57.3 (23.3)	50.8 (20.6)	62.9 (24.7)
Participants with >=1 SAE (%)	39	16 (41.0)	8 (38.1)	8 (44.4)

BI: Barthel Index; EQ: EuroQol; ICH: intracranial haemorrhage; mRS: modified Rankin Scale; NIHSS: National Institutes of Health stroke scale; Neuro. det.: neurological deterioration; t-MMSE: Modified telephone Mini-Mental State Examination; SAE: serious adverse event; TICS-M: Modified Telephone Interview for Cognitive Status; VAS: Visual Analogue Scale; ZDS: Zung Depression Scale.

Definitions:

‡ Clinical events determined by the investigator: recurrent stroke, sICH, hypotension, hypertension

National Institutes Health stroke scale (NIHSS): 0 (normal neurological status) to 42 (coma with quadriplegia), 43 (death)

Neurological deterioration: increase in NIHSS > 4

Dysphagia severity rating scale: 0 (normal oral intake), 12 (nil by mouth), 13 (death)

Barthel Index: -5 (death) to 0 (severe disability) to 100 (no disability)

Modified telephone Mini-Mental State Examination (t-MMSE): -1 (death), 0 (severe dementia) to 18 (normal).

Modified Telephone Interview for Cognitive Status (TICS-M): -1 (death, 0 (severe dementia) to 37 (normal).

Verbal fluency (number of animals named in one minute): -1 (death), 0 (none named) to infinity.

Health utility status (HUS, derived from European Quality of Life-5 dimensions, EQ-5D): -0.5 (very poor quality of life, 0 (death) to 1.0 (perfect quality of life)

European Quality of Life-Visual Analogue Scale (EQ-VAS): -1 (death), 0 (very poor) to 100 (excellent)

Zung Depression Scale (ZDS): 0 (normal), 100 (severe depression) to 102.5 (death)

Serious adverse events

Data are number (%).

	All	All GTN	Sham
Participants	39	21	18
Number of SAEs	24	9	15
Treatment relationship			
Before	0 (0.0)	0 (0.0)	0 (0.0)
During	22 (91.7)	8 (88.9)	14 (93.3)
After	2 (8.3)	1 (11.1)	1 (6.7)
Relationship to treatment			
Not related	2 (8.3)	1 (11.1)	1 (6.7)
Improbable	14 (58.3)	4 (44.4)	10 (66.7)
Possible	6 (25.0)	3 (33.3)	3 (20.0)
Probable	1 (4.2)	0 (0.0)	1 (6.7)
Definite	1 (4.2)	1 (11.1)	0 (0.0)
Organ			
Cardiovascular	8 (20.5)	4 (19.0)	4 (22.2)
Nervous system	4 (10.3)	1 (4.8)	3 (16.7)
Respiratory	5 (12.8)	1 (4.8)	4 (22.2)
Gastrointestinal	2 (5.1)	1 (4.8)	1 (5.6)

Genitourinary	1 (2.6)	0 (0.0)	1 (5.6)
Haematological/Immunological	0 (0.0)	0 (0.0)	0 (0.0)
Metabolic/Endocrine	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal/Cutaneous	1 (2.6)	0 (0.0)	1 (5.6)
Miscellaneous	3 (7.7)	2 (9.5)	1 (5.6)
Any SAE	16 (41.0)	8 (38.1)	8 (44.4)