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Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2): Assessment of safety and efficacy of transdermal glyceryl trinitrate, a nitric oxide donor, and of the feasibility of a multicentre ambulance-based stroke trial

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SYNOPSIS

Title	Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2): Assessment of safety and efficacy of transdermal glyceryl trinitrate, a nitric oxide donor, and of the feasibility of a multicentre ambulance-based stroke trial.
Acronym	RIGHT-2
Short title	Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2
Chief Investigator	Professor Philip Bath
Objectives	To determine whether glyceryl trinitrate improves outcome in patients with ultra-acute stroke
Trial Configuration	Multicentre prospective randomised single-blind blinded-endpoint parallel group trial
Setting	Initial treatment in ambulance followed by treatment in secondary specialist stroke centre
Sample size estimate	A total sample size of 1300 participants (two arms each of 650 per group) is required, assuming 5% overall significance (2-tailed); power 90%; odds ratio (OR) =0.70; treatment crossovers =2%; losses to follow-up =3%; a reduction for baseline covariate adjustment =20%; and a non-stroke proportion of 34%
Number of participants	1300 patients: 650 patients randomised to GTN; 650 patients randomised to no GTN
Eligibility criteria	**Inclusion criteria:** • Patients presenting to paramedics in context of 999 ambulance call for 'stroke'. • Age 18 years or more. • 'Face/Arm/Speech' Time (FAST) score 2 or more • Time <=4 hours of onset. • Systolic BP >=120 mmHg. • Paramedic is trained in RIGHT-2 procedures, is from a participating ambulance station, and will take patient to a participating comprehensive/primary stroke centre. • Written or witnessed oral consent, or relative/paramedic proxy assent **Exclusion criteria:** • Patient at a Nursing Home. • Glucose (BM stix) <2.5 mmol/l. • Glasgow Coma Scale <8 • Witnessed seizure/fit at presentation. • Known life expectancy <6 months. • Known to have taken a PDE5 inhibitor, such as sildenafil, in previous day before stroke. • Known sensitivity to Transiderm Nitro patch. • Known sensitivity to Duoderm hydrocolloid dressing.

	• Known previous enrolment into RIGHT-2.
Description of interventions	Active: Transdermal glyceryl trinitrate patch (GTN), 5mg applied daily for 4 days Control: Sham patch, applied daily for 4 days
Duration of study	The trial will last 48 months with recruitment occurring over 29 months. Once enrolled, participants will be treated for 4 days, and followed-up at 90 (primary outcome) and 365 days.
Randomisation and blinding	Patients will be randomised (1:1) to receive either glyceryl trinitrate patches or sham patches. Randomisation will be performed by the Nottingham Stroke Trials Unit (STU) and identical looking numbered treatment packs sent in blocks to each ambulance station. Patients and outcome assessors will be masked to treatment allocation.
Outcome measures	**Primary outcome** Death/dependence/independence: 7-level modified Rankin Scale (mRS) 90 days after stroke. **Secondary outcomes** Hospital admission: • Neurological impairment - National Institutes of Health Stroke Scale (NIHSS). • Systolic and diastolic blood pressure, heart rate. • Proportion of participants with systolic blood pressure <185 mmHg. • Stroke lesion size on brain scan (CT or MR). • Amount of cerebral arterial patency on brain scan (CT or MR angiography). Use and timing of hyperacute and acute treatments in hospital: • Open-label blood pressure lowering • Intravenous thrombolysis • Mechanical reperfusion • Hemicraniectomy • Surgery for intracerebral haemorrhage • Days in intensive/critical care unit At day 2-4: • Systolic and diastolic blood pressure, heart rate The following will be measured on a plain brain scan (CT or MR): • Size of infarct/haematoma • Hyper-attenuated artery sign • Infarct swelling • Mass effect • Secondary haemorrhagic transformation of infarct At day 4 (or discharge if sooner): • Stroke recurrence • Neurological impairment (NIHSS).

	• Neurological deterioration from baseline (NIHSS >=4 points, or >=2 point increase in any domain). • Infection (pneumonia/chest, urinary tract, other). • Dysphagia requiring altered food or enteral tube At discharge/death • Length of stay in hospital. • Patient disposition (died, institution/in hospital, home). At days 90 and 365 by telephone (or post): • Dependency – modified Rankin Scale (primary end point at Day 90) • Disability/Activities of Daily Living - Barthel Index (BI). • Quality of life - Health Utility Status (HUS, derived from EuroQoL-5D), EQ-Visual Analogue Scale (EQ-VAS). • Cognition – Adult lifestyles and function interview (ALFI)-MMSE, Telephone Interview Cognition Scale (TICS), animal naming. • Mood - Zung Depression Scale. • Patient disposition (died, institution/in hospital, home). • Stroke recurrence.
Statistical methods	The effect of GTN versus no GTN will compare the distribution in mRS scores (shift in mRS) at day 90. The analysis will be by intention-to-treat using ordinal logistic regression (OLR), adjusted for baseline prognostic factors. The assumption of proportional odds will be tested using the likelihood ratio test.

ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
A&E	Accident & Emergency
AI	Augmentation Index
ASPECTS	Alberta Stroke Program Early CT score
BI	Barthel Index
BP	Blood pressure
CE	Cardio-embolic
CF	Informed Consent Form
CI	Chief Investigator
CRF	Case Report Form
CT	Computerised Tomography
CTA	CT angiography
CTP	CT perfusion
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
eCRF	Electronic CRF
ED	Emergency Department
EMAS	East Midlands Ambulance Service
EQ-5D	Euro Quality of Life-5 Dimensions
EQ-VAS	Euro Quality of Life-Visual Analogue Scale
EOT	End of Trial
FAST	Face, Arm, Speech, Time test
GCP	Good Clinical Practice
GTN	Glyceryl Trinitrate
HR	Heart Rate
HUS	Health Utility Status
ICH	Intracerebral Haemorrhage
IS	Ischaemic Stroke
ITT	Intention to treat
LACS	Lacunar syndrome
LAD	Large artery disease
MHRA	Medicines and Healthcare products Regulatory Agency
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance imaging
MRA	MR angiography
mRS	Modified Rankin Scale
NHS	National Health Service
NIHSS	National Institutes of Health Stroke Scale
NK	Not Known
NO	Nitric oxide
NTG	Nitroglycerin
NUH	Nottingham University Hospitals NHS Trust
PACS	Partial anterior circulation syndrome
PI	Principal Investigator (at a local centre)
PIS	Participant Information Sheet
POCS	Posterior circulation syndrome
PP	Per protocol
REC	Research Ethics Committee
R&D	Research and Development department

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SBP	Systolic Blood Pressure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVD	Small vessel disease
TACS	Total anterior circulation syndrome
TCD	Transcranial Doppler
TIA	Transient Ischaemic Attack
TICS	Telephone Interview Cognition Scale
TMC	Trial Management Committee
TSC	Trial Steering Committee
UoN	University of Nottingham
ZDS	Zung Depression Scale

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Stroke is common (life-time risk 1/6) and devastating (death 25%, dependency 40% at 1 year). Acute treatment is limited to alteplase,[1] aspirin, hemicraniectomy and stroke unit care. Anticoagulation is ineffective,[2] neuroprotection unproven,[3, 4] and there is no specific treatment for ICH. Developing new interventions in hospitals has failed, in part, due to delayed treatment beyond the 'golden' hour after stroke. The management of physiological disequilibrium - BP,[5] oxygen, glucose,[6] cerebral oedema - remains unclear, and it is reasonable to hypothesise that their treatment should start rapidly after stroke onset.

High blood pressure is common (80%) in patients with acute IS and ICH, and is associated independently with increased early recurrence and late death or dependency.[7-9] Whether lowering BP will improve outcome, or worsens it through reducing cerebral blood flow (due to dysfunctional autoregulation) remains unclear; completed trials of drugs that lower BP have focussed on hospitalised patients with hyperacute or acute stroke although most started treatment many hours after onset. When assessing functional outcome, trial results have varied from a strong positive trend (INTERACT-2: SBP 14 mmHg lower with intensive treatment in ICH [10]) through neutral effect (IMAGES: BP 4/3 mmHg lower with intravenous magnesium in mixed IS/ICH;[3] CATIS: SBP 9 mmHg lower with intensive treatment in IS [11]) to strong negative trend (BEST: oral propranolol or atenolol in mixed IS/ICH;[12] INWEST: intravenous nimodipine in IS;[13, 14] SCAST: BP 5/2 mmHg lower with oral candesartan in mixed IS/ICH [5]). Meta-analysis, and meta-regression of trial outcomes versus BP change, have not identified benefit.[15, 16] Two large hospital-based hyperacute trials are currently recruiting patients: ATACH-2 [ICH], ENCHANTED [IS].

Nitric oxide donors are a candidate treatment for the treatment of acute stroke through, potentially lowering BP, neuroprotection and reperfusion. Several NO donors are licensed in the UK and are used widely in patients with ischaemic heart disease, heart failure and severe hypertension; these include intravenous sodium nitroprusside and transdermal glyceryl trinitrate. One uncontrolled pilot study found that sodium nitroprusside lowered BP without altering cerebral perfusion (assessed using CT SPECT), and attenuated platelet function, in patients with recent ischaemic stroke.[17] Four phase II randomised controlled trials assessed transdermal glyceryl trinitrate in patients with acute stroke (IS and ICH) (Table 1).

Table 1. Characteristics of completed trials of transdermal glyceryl trinitrate.

	GTN-1 [18]	GTN-2 [19]	GTN-3 [20]	RIGHT [21-23]	ENOS [24-27]
Setting	Hospital	Hospital	Hospital	Pre-hospital	Hospital
Time window (hr)	<120 hours	<72 hours	<120 hours	<4 hours	<48 hours
Stroke type	IS/ICH	IS/ICH	IS/ICH	IS/ICH	IS/ICH
SBP range (mmHg)	No limits	100-230	140-220	>140	140-220
Treatment blinding	Double-blind	Open-label	Single-blind	Single-blind	Single-blind
GTN daily dose (mg)	5	5/10	5	5	5
Thrombolysis	N/A	N/A	N/A	After GTN	Before GTN
Sample size					
Intended	38	90	18	80	≥ 3500
Achieved	37	90	18	41	4011

ICH: intracerebral haemorrhage; IS: ischaemic stroke; N/A: not applicable; SBP: systolic blood pressure

GTN lowered BP, increased heart rate, and did not alter cerebral blood flow (assessed using xenon CT) or platelet function.[18-23] In one of these trials (RIGHT), treatment was initiated in the pre-hospital/ambulance setting with randomisation occurring within 4 hours; treatment with GTN was associated with improved functional outcome (mRS).[22]

The safety and efficacy of GTN in patients with acute stroke (IS, ICH) was assessed in the large international MRC ENOS phase III trial.[26] In comparison with no GTN, transdermal GTN was not associated with any difference in functional outcome (mRS), disability/Activities of Daily Living (BI), cognition (tMMSE, TICS, animal naming), mood (ZDS) or quality of life (EQ-5D/HUS, EQ-VAS).[26] No safety issues were found with GTN. In the subgroup of patients randomised within 6 hours of ictus (identified here as 'ENOS-early'), treatment with GTN was associated with reduced death, and improved functional outcome (mRS, BI) and quality of life (Table 2).

Table 2. Outcomes in 273 patients treated within 6 hours of stroke with GTN versus no GTN in ENOS-early. Unpublished data.
Data are number (%), median [interquartile range] or mean (standard deviation). Analysis with binary logistic regression (odds ratio), ordinal logistic regression (odds ratio) or multiple regression (mean difference).

Outcome measure	GTN	No GTN	OR/MD (95% CI)	p
Modified Rankin Scale (/6)	3 [3]	3 [3]	0.53 (0.34, 0.82)	<0.001
Barthel Index (/100)	74 (34)	60 (41)	14 (4.6, 22.5)	0.01
EQ-VAS (/100)	62 (29)	53 (35)	9.6 (1.8, 17.5)	0.03
Death (%)	11 (7.6)	26 (20.2)	0.35 (0.13, 0.96)	0.04

CI: confidence intervals; EQ-VAS: EuroQoL-Visual Analogue Scale; ICH: intracerebral haemorrhage; IS: ischaemic stroke; MD: mean difference; N/A: not applicable; OR: odds ratio; SBP: systolic blood pressure

The following summary observations can be made based on data from the five GTN trials:

- Transdermal administration is advantageous since oral treatment is confounded by dysphagia in 50% of patients with acute stroke, whilst intravenous therapy requires intensive monitoring. Additionally, treatment can be stopped and restarted according to need.
- Peak concentrations are achieved by 1-2 hours.[28]
- GTN lowers systolic BP significantly by 15, 60 and 120 minutes.[20, 22]
- GTN lowers central and peripheral SBP, DBP and pulse pressure; peak systolic BP and augmentation index; and 24 hour BP in both dipping and non-dipping patients.[19, 20, 22, 29, 30]
- GTN is feasible to administer, tolerated, and safe when given early after acute stroke.[19, 20, 22, 29]
- GTN does not alter platelet function so it can be given in ICH as well as IS.[29]
- GTN does not reduce cerebral blood flow.[19, 20]
- GTN is safe in patients with severe carotid stenosis.[31]
- GTN is safe.[26]

In a meta-analysis of individual patient data from the 5 GTN trials, and in patients treated within 6 hours (data from ENOS-early and RIGHT):

- The effect of GTN on functional outcome appears to be time-dependent; outcome is unaffected beyond 6 hours (Figure 1).
- GTN is associated with reduced death (Figure 2).
- Very early administration before 4-6 hours may improve functional outcome, cognition and mood (Table 3).[22, 26]

Figure 1. Meta-analysis of effect of GTN versus no GTN on mRS by time from stroke to randomisation.

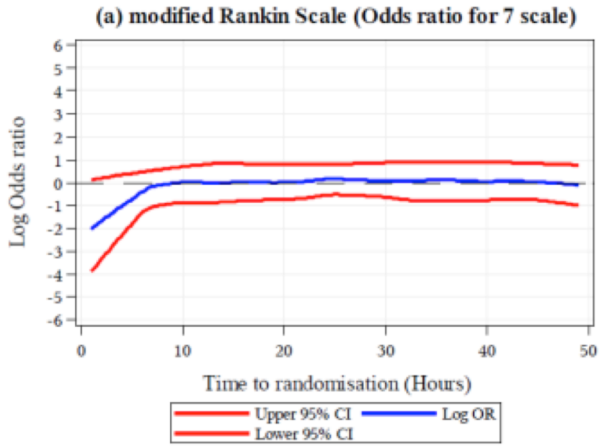


Figure 2. Meta-analysis of effect of GTN versus no GTN on end of trial death. Data from RIGHT and ENOS-early.

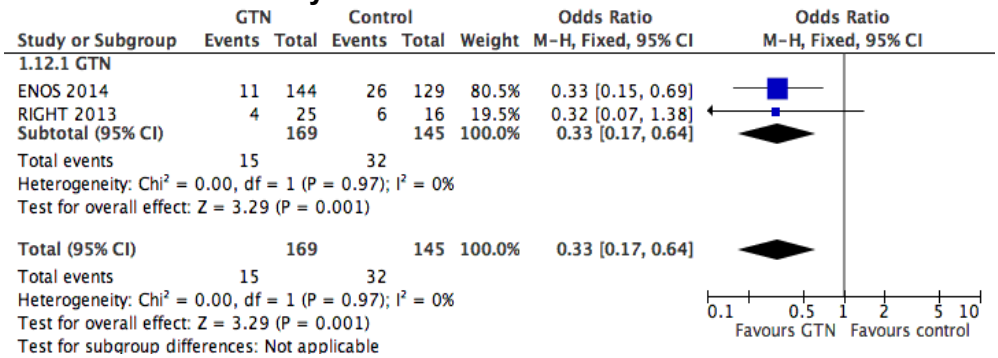


Table 3. Effect of GTN versus no GTN on outcomes using individual patient data from ENOS-early and RIGHT.

	mRS	BI	HUS	EQ-VAS	tMMSE	TICS-M	ZDS
OR/MD	0.51	9.0	0.06	6.0	1.44	3.96	-0.84
95% CI	0.33, 0.77	26.0, 15.5	0.00, 0.12	-0.3, 12.3	0.41, 2.46	1.42, 5.95	-13.6, -3.3
p	0.002	0.006	0.07	0.06	0.006	0.001	0.001

Multiple mechanisms exist by which NO/GTN might be effective if given very early after stroke; taken together, these actions may 'buy time' for the brain, protect it and prime patients for arterial reperfusion therapies:

- NO/GTN lowers BP in acute/subacute stroke [32] and so may 'move' patients down the epidemiological curve relating high BP and poor outcome.[7] This mechanism may be of particular relevance in ICH.

- NO dilates cerebral arteries (e.g. middle cerebral) so could increase 'front door' cerebral blood flow (CBF) and peri-lesional perfusion, as seen in the GTN-3 pilot trial.[20]
- NO dilates pial arteries (shown experimentally [33]) so might increase CBF via the 'back-door'.
- NO donors are neuroprotective in preclinical stroke,[34] especially if given ultra-early.
- Endogenous NO levels are low in acute stroke;[35] administration will supplement low [NO].
- GTN may 'prime' patients for rt-PA by lowering their BP so that more can be treated, and more rapidly after hospital arrival. RIGHT showed non-significant trends for these.[22]
- GTN, through cerebral vasodilation, may increase access of alteplase to obstructing clot and therefore increase the effectiveness of thrombolysis, i.e. GTN might be additive to rt-PA.

Paramedic care is based on 'ABC' stabilisation, diagnosis, and rapid transport to hospital. Paramedics are used to giving potent interventions (thrombolysis for MI; morphine for pain) and doing trials in non-stroke (thrombolysis - MI,[36] bronchodilators - asthma). Starting treatment before hospital can drastically reduce time to treatment (45 mins in MI [36]) so increasing the proportion of patients treated within the 'golden' hour.

Since stroke is common and can be devastating, and proven treatments are only hospital-based, future treatments may have to be tested much earlier in the pre-hospital period. Several ambulance-based stroke trials have been conducted (Table 3):

- FAST-Mag pilot – This, the first ambulance-based stroke study, studied ultra-acute administration of magnesium (putative neuroprotectant, see IMAGES [3]) in 20 US patients; a hospital-based doctor took consent via mobile phone (since US paramedics may not take such consent) whilst paramedics gave treatment.[37]
- FAST-Mag – This is the largest completed ambulance stroke trial and studied administration of intravenous magnesium within 2 hours of stroke in 1,700 patients (phase III RCT) from 60 sites in Los Angeles/Orange County (Savers J. ISC/ASA Conference 2014). Uniquely, the trial demonstrated the feasibility of performing a large multicentre ambulance-based stroke trial. Although magnesium was safe, no efficacy was seen. In a qualitative study, paramedics found the experience of taking part in a large trial to be positive.[38]
- PIL-FAST - A phase IIa trial in Newcastle that compared the feasibility (recruitment, quality of data collection) of performing ambulance-based trials; it tested the safety of sub-lingual lisinopril in 14 patients (Table 4) within 3 hours (+arm weakness, systolic BP>160 mmHg) who were admitted to one of 3 hospitals.[39] Lisinopril lowered BP.[40]
- RIGHT – See above and tables 1 and 4.
- Other trials – These have assessed brain scanning in the ambulance (this leading to accelerated time to thrombolysis),[41, 42] and administration of insulin and per-conditioning.[43, 44]

Table 4. Trial and baseline patient characteristics in ambulance-based trials and ENOS-early.
Unpublished summary of published data.

Trial: intervention	Size	Time Min	Av. time min	Age yr.	Male %	IS %	ICH %	TIA %	Mimic %	SBP mmHg
FAST-Mag pilot: Mg [37]	20	<720	206	74	50	80	4	0	0	-
FAST-Mag: Mg *[ISC 2014]*	1700	<120	45	69	58	62	22	13	3	-
PIL-FAST: Lisinopril [39, 40]	14	<180	77	73	50	64	21	7	7	185
RIGHT: GTN [21, 22]	41	<240	55	79	54	66	15	7	12	168
ENOS-early: GTN	273	<360	276	70	56	77	22	-	1	167

These pre-hospital trials found that (Table 5):

- Treatment could be started much earlier, e.g. in the ultra-acute period with an average of 45 minutes in FAST-Mag and 55 minutes in RIGHT.
- Large multicentre trials can be performed (FAST-Mag).
- A recruitment rate of 1 - 2 patients per month per city is feasible in the UK (PIL-FAST, RIGHT).
- Together, PIL-FAST and RIGHT suggest that small ambulance-based trials are feasible in the UK. Evidence is now needed to test this approach in a large trial involving multiple ambulance services and acute hospitals across the UK.
- Paramedics value participating in stroke trials (FAST-Mag, RIGHT).[23, 38]

Table 5. Logistics in ambulance-based trials.
Unpublished summary of published data. NK: not known.

	Stations	Paramedics	Enrol/Screen	Rate/month	NIHSS	rt-PA
FAST-Mag pilot [37]	3	NK	20 / 28	?	11	-
FAST-Mag *ISC 2014*	60	3000	-	18	11	27%
PIL-FAST [39, 40]	NK	NK	NK	1.0	4	?
RIGHT [21, 22]	11	75	41 / 92	1.9	~9	24%

RIGHT-2 will assess the safety and efficacy of pre-hospital ambulance-based paramedic-delivered GTN when administered ultra-acutely after stroke. Whilst ambulance-based paramedic-delivered stroke trials have been done in the UK in single site pilot trials (PIL-FAST, RIGHT [21, 22, 39, 40, 45]), they have not been done across multiple ambulance services and hospital sites in the UK. Although the FAST-Mag trial showed that the approach is possible in 1,700 patients in the US (presentation at International Stroke Trial, 2014), there are multiple differences in the way pre-hospital care is administered between the UK and US.

Four of the five GTN trials had a lower limit for systolic blood pressure, either >=100 mmHg [19] or >=140 mmHg;[20, 22, 26] the first study had no lower limit.[29] Since several potential mechanisms by which GTN might work are BP-independent, RIGHT-2 will include patients with high-normal BP as well as high BP, with a lower limit set to >= 120 mmHg. This has the

advantage that the results will apply to a wider population of stroke patients and include more patients with severe stroke (some of whom have SBP <140 mmHg).

DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

Description
The investigational medicinal product (IMP) is transdermal glyceryl trinitrate patch (GTN, - Transiderm Nitro '5' (Novartis). GTN is also known as nitroglycerin (NTG). One patch will be given on 4 consecutive days. Further chemical and pharmacological properties of the GTN patch - Transiderm Nitro '5' are provided in a separate Summary of Product Characteristics document (SmPC).

The GTN patch will be placed on the shoulders or back and the position rotated daily. GTN patches will be covered with a gauze dressing to mask the patient to treatment.[20, 21, 24]

Manufacture
The GTN patch Marketing Authorisation Holder is Novartis Pharmaceuticals Ltd.

Packaging and labelling
Active patches will not be removed from their primary packaging. For blinding purposes, active patches will be packed with a gauze dressing into a plain opaque pouch which will be heat sealed by Pharmacy Production, Nottingham University Hospitals NHS Trust MIA(IMP): 19162. The manufacture will be in accordance with cGMP. Groups of 4 pouches will be assigned a pack number and these 4 will be packed into a labelled carton with the same pack number. The outer pouches and carton will be labelled according to Annex 13 - the Rules Governing Medicinal Products in the European Union, Volume 4. Labels will state usage instructions and storage conditions for the IMP.

The information sheets and consent forms will separate from the sealed package to allow participation to be considered without seals being broken.

The final product will be QP released by the designated person to provide blinded trial treatment packs for use in the trial.

Further details of the manufacture of the blinded packs of patches will be provided in a separate simplified IMPD.

Storage, dispensing and return
NUH Clinical Trial Pharmacy will act as the central distribution pharmacy and receive and store blinded packs from Pharmacy Production. Pharmacy will send packs to the central Ambulance Service for distribution to Ambulance Stations where available. Where not available, packs will be sent to individual ambulance stations. The packs will accompany each patient in the ambulance and hospital, with appropriate tracking.

Packs will be stored in each Ambulance Station in a secure environment as per storage of drugs. As IMP is stored according to standard clinical practice, no monitoring of storage temperatures will take place. Each participating paramedic will take and sign-out one pack at the start of duty. If unused during their shift, the paramedic will return and sign-in the pack. When a pack is assigned to a participant, the paramedic will add the Participant name and date dispensed to the label. If the pack has been assigned, the paramedic will complete the Use/Non-use Form. If the pack has been assigned but the IMP was not used (eg if the participant changed their mind after consenting but before application of the patch), the

paramedic will explain on the Use/Non-use Form why treatment was not administered, and return the pack to the Coordinating Pharmacy in Nottingham via their Ambulance Service.

Trial treatment must not be used for any other purpose than the present study. Any part-used packs at the ambulance stations will be returned to NUH for disposal. Any part used packs at the admitting hospital will be returned to the local pharmacy for disposal according to their local procedures. Returned trial medication that has been assigned to a participant must not be re-dispensed to a different participant.

Known Side Effects

Table 6. Known side effects of the IMP

Nervous System Disorders:	
Common:	Headache
Very rare:	Dizziness
Cardiac Disorders:	
Rare:	Tachycardia
Vascular Disorders:	
Rare:	Orthostatic hypotension, flushing
Gastrointestinal Disorders:	
Very Common:	Nausea, vomiting
Skin and subcutaneous tissue disorders:	
Uncommon:	Contact dermatitis
General disorders and administration site conditions:	
Uncommon:	Application site erythema, pruritus, burning, irritation.
Investigations:	
Rare:	Heart rate increase

NB. Very common (≥ 1/10); common (≥ 1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥ 1/10,000, <1/1000); very rare (<1/10,000), including isolated reports.

Contraindications to the IMP are as follows:

- Known hypersensitivity to glyceryl trinitrate/nitroglycerin, and related organic nitrates or any excipient.
- Acute circulatory failure associated with marked hypotension (shock).
- Conditions associated with elevated intracranial pressure.
- Myocardial insufficiency due to obstruction, as in aortic or mitral stenosis, or constrictive pericarditis.
- Concomitant use with a phosphodiesterase type 5 (PDE5) inhibitor such as sildenafil (Viagra®) because PDE5 inhibitors may amplify the vasodilatory effects of GTN resulting in severe hypotension.
- Severe hypotension (systolic blood pressure less than 90 mmHg).
- Severe hypovolaemia.

The following interactions are possible:

- Concomitant administration with other vasodilators e.g. PDE5 inhibitors such as sildenafil potentiate the blood pressure lowering effects of GTN.

- Concomitant treatment with calcium antagonists, ACE inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants and major tranquillisers may potentiate the blood pressure-lowering effect of GTN, as may alcohol.
- Concurrent administration with dihydroergotamine may increase the bioavailability of dihydroergotamine. This warrants special attention in patients with coronary artery disease, because dihydroergotamine antagonises the effect of GTN/nitroglycerin and may lead to coronary vasoconstriction.
- Non-steroidal anti-inflammatory drugs, except acetyl salicylic acid, may diminish the therapeutic response of Transiderm Nitro.
- Concurrent administration with amifostine and acetyl salicylic acid may potentiate the blood pressure lowering effects of Transiderm Nitro.

Reference source: SPC:
http://www.medicines.org.uk/emc/medicine/1333/SPC/Transiderm-Nitro+5+and+10

Placebo
There is no matching placebo. The control group will not receive GTN, and matching placebo GTN patches are not available. Instead, a sham patch of similar size to the GTN patch (Duoderm – a hydrocolloid dressing of size 4.4cm x 3.8cm) will be used, Like the GTN patch, it will be placed on the shoulders or back and the position rotated daily. Duoderm patches are manufactured by Convatec and are presented in individually wrapped packages. They do not have identifying information on them. Sham-Duoderm patches will be covered by a gauze dressing to conceal treatment allocation.[20, 21, 24]

Trial packaging
The placebo packs will be manufactured, supplied, packaged, labelled and QP released to provide blinded treatment packs and distributed in the same way as the active IMP. Storage, dispensing and return of the sham patch will be the same as the active IMP.

Known side effects of placebo patches
There is the possibility of allergic reactions to the product or its components. Patients who have a known sensitivity or allergy to the product or its components should therefore not participate in the study.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE
The purpose of the study is to determine whether early use of GTN within 4 hours of suspected ultra-acute stroke, and continuing administration once daily for a further three days, is associated with improved outcome.

PRIMARY OBJECTIVE
To determine whether GTN is safe and reduces death or dependency after stroke when administered within 4 hours of stroke onset.

SECONDARY OBJECTIVES
- To determine whether GTN reduces disability, low mood, poor cognition and low quality of life
- To determine whether GTN improves blood flow, enhances dissolution/clearing of thrombus in ischaemic stroke, reduces haematoma enlargement in haemorrhagic stroke, and reduces lesion size, as determined with plain CT, and CTA.

- To determine the feasibility of conducting a multi-centre UK ambulance-based stroke trial.

ADDITIONAL RESEARCH OBJECTIVES

- To investigate whether specific genetic characteristics are associated with outcome
- To investigate whether there is a difference in trans-cranial Doppler measurements between the two groups
- To investigate whether there is a difference in augmentation index between the two groups.
- To investigate whether there is a difference in blood biomarkers (such as S-100 / nitric oxide (NOx) / P-selectin) between the two groups and whether biomarkers may be associated with outcome.
- To investigate whether there is a difference between the two groups in blood pressure measured using 24 hour ambulatory blood pressure monitoring.
- To explore experiences and perspectives of patients, ambulance staff and hospital staff including ethical issues of conducting ambulance trials. This will be limited to patients and paramedics within the East Midlands region (Appendix L).
- To explore the experiences of Paramedics taking part in research activity in ambulance services participating in RIGHT-2 (Appendix M).

The above will all be measured in a subset of patients and Paramedics and will be reported separately from the main trial analyses. Consent to participate in any of the above is optional.

TRIAL / STUDY DESIGN

Prospective multicentre parallel-group randomised single-blind blinded-endpoint controlled trial.

TRIAL / STUDY CONFIGURATION

The study is a prospective multicentre parallel-group randomised single-blind blinded-endpoint controlled trial of GTN versus no GTN given initially a maximum of 4 hours after stroke, and then given every 24 hours for the next 3 days. It will be conducted by the ambulance service and the secondary care centres participants are admitted to.

The study will provide the option for centres to collect additional information if the participant provides separate consent. Participation by both centre and participant is optional.

Primary endpoint

The primary end point of the study is the 7-level modified Rankin Scale (mRS, appendix A) 90 days after the participant's stroke.

Secondary endpoints

Hospital admission:

- Neurological impairment (NIHSS)
- Systolic and diastolic blood pressure, heart rate.
- Proportion of participants with systolic blood pressure <185 mmHg.
- Stroke lesion size on brain scan (CT or MR).
- Amount of cerebral arterial patency on brain scan (CT or MR angiography).

Use and timing of hyperacute and acute treatments in hospital:

- Open-label blood pressure lowering.
- Intravenous thrombolysis.
- Mechanical reperfusion.
- Hemicraniectomy.
- Surgery for ICH.
- Days in intensive/critical care unit.

At day 2-4:

- Systolic and diastolic blood pressure, heart rate.

The following will be measured on a plain brain scan (CT or MR):

- Infarct/haematoma size.
- Hyper-attenuated artery sign.
- Infarct swelling
- Mass effect.
- Secondary haemorrhagic transformation of infarct.

At day 4 (or discharge if sooner):

- Neurological impairment (NIHSS).
- Stroke recurrence.
- Neurological deterioration from baseline (NIHSS >=4 points, or >=2 point increase in any domain).
- Infection (pneumonia/chest, urinary tract, other).
- Dysphagia.

At discharge/death

- Length of stay in hospital.
- Patient disposition.

At days 90 and 365 by telephone (or post):

- Dependency – modified Rankin Scale (primary end point at Day 90).
- Disability/Activities of Daily Living - Barthel Index (BI).
- Quality of life - Health Utility Status (HUS, derived from EuroQoL-5D), EQ-Visual Analogue Scale (EQ-VAS).
- Cognition - telephone-MMSE, Telephone Interview Cognition Scale (TICS), animal naming.
- Mood - Zung Depression Scale.
- Patient disposition (died, institution/in hospital, home).
- Stroke recurrence.

Additional research end points

- Middle cerebral artery blood flow measured by transcranial Doppler as soon as possible after admission, up to and including day 3.
- Central systemic blood pressure and augmentation index using pulse wave analysis at the radial artery at the wrist as soon as possible after admission, up to and including day 3.
- Blood pressure as measured using 24 hour ambulatory monitoring as soon as possible after admission, up to and including day 3.

In addition, investigation of blood biomarkers such as S-100, NOx and P-selectin and their potential association with efficacy will be performed and reported separately from the main trial results. Similarly, blood taken for genetic investigation will be stored and analysed for reporting independently of the main trial results.

The additional research end points will only be available in a subset of patients since not all centres will have the equipment available, and all measures are subject to additional consent.

Qualitative data from patients within the East Midlands discharged to the community and EMAS NHS Trust Paramedics involved in the trial will be sought to explore their experiences and perspectives of participation with a specific focus on ethical issues such as consent for the additional research objectives detailed in Appendix L.

Qualitative data from Paramedics involved within all participating ambulance trusts will be sought explore the experiences of participation in ambulance-based trials to inform the objectives detailed in Appendix M. Data collection will stop at the end of the recruitment phase of the main trial.

Safety endpoints

By day 4

- Any serious adverse event.
- Headache.
- Infection (pneumonia/chest, urinary tract, other).
- Dysphagia
- Hypotension requiring clinical intervention.
- Hypertension requiring clinical intervention.

From day 5 to day 365

- Any fatal serious adverse event.

Data on stroke recurrence and acute coronary syndrome, termed safety outcome events, will be collected up to day 90.

Stopping rules and discontinuation

The DMC review unblind data twice yearly in respect of safety and efficacy, and consider the study in the context of other trials of altering BP in stroke. Stopping rules are based on the Haybittle-Peto rule as a guide for proof beyond reasonable doubt for:

Safety

- Poor outcome (modified Rankin Scale >2) is less frequent in the sham/control group, P<0.01 (nominal, 2-sided); OR
- Death is less frequent in the sham/control group, P<0.01 (nominal, 2-sided)

Efficacy

- Poor outcome (modified Rankin Scale >2) is less frequent in the GTN/active group, P<0.01 (nominal, 2-sided); AND
- Death is less frequent in the GTN/active group, P<0.01 (nominal, 2-sided); AND
- Poor outcome (modified Rankin Scale >2) is less frequent in the GTN/active group in ischaemic stroke, P<0.01 (nominal, 2-sided); AND

- Poor outcome (modified Rankin Scale >2) is less frequent in the GTN/active group in intracerebral haemorrhage, P<0.05 (nominal, 2-sided).

The extreme stopping rules for efficacy are designed to persuade practitioners that such a simple and inexpensive treatment can modify outcome.

The DMC also monitor SAEs and neurological deterioration, and outcomes in particular subgroups of patients including those with severe stroke (TACS (Bamford, Sandercock et al. 1991)), BP <140 mmHg. or with significant carotid disease (ipsilateral stenosis of the internal carotid artery >50%).

RANDOMISATION AND BLINDING

A randomisation sequence will be generated using random permuted fixed-size blocks stratified by ambulance station. NUH pharmacy will prepare opaque treatment packs containing either a GTN or sham patch, and a gauze dressing. 4 of these packs will be contained within a larger pack containing Information Sheet, Consent Form and CRF.

Maintenance of randomisation codes and procedures for breaking code

In order to minimise selection bias, a participant must be enrolled in the study before the envelope containing the treatment package is opened. There will only be one treatment package available in the ambulance at any one time. Ambulance stations will be sent blocks of GTN/sham treatment packs for distribution to ambulances.

Although both the GTN and sham patches have no identifying information on them, they look slightly different and it will be obvious to the paramedic (in the ambulance) and nurses (in hospital) what they are administering. Since GTN and sham patches will be placed on the participant's shoulder or back, it will be difficult for them to recognise the treatment that they have received.

In order to minimise bias that could be introduced through knowledge of what the participant has received, unmasked staff will be kept to a minimum and be asked not to reveal the treatment to anyone. In addition, the primary end-point of the study will be recorded by personnel masked to treatment assignment.

Unblinding

If there is an emergency situation where further treatment of the participant is dependent on knowledge of the administered treatment, unblinding can be performed by review of the patch on the participant's shoulder or back.

TRIAL MANAGEMENT

Day-to-day management of the trial will be the responsibility of the Trial Management Committee (TMC). The TMC will report to the Trial Steering Committee (TSC). An independent Data Monitoring Committee (DMC) will monitor the safety of participants, and will advise the TSC on safety. Trial co-ordination will pass through the Nottingham Stroke Trials Unit and members of the TMC.

The Chief Investigator has overall responsibility for the study and shall oversee all study management. The data custodian will be the Chief Investigator.

Trial Management Committee (TMC)

The Trial Management Committee will include the Trial Manager (who will chair meetings), Chief Investigator, Trial Coordinators, National Paramedic, Trial Statistician, Trial Programmer, and other project staff. This group, based at the Nottingham Stroke Trials Unit,

will meet regularly, at least every four weeks. The TMC will communicate regularly by teleconference with Ambulance Service Paramedic Champions, and Image data management staff in Edinburgh, as required.

Trial Steering Committee (TSC)
The Trial Steering Committee will provide oversight of the trial. It will meet (in person or by telephone conference) prior to commencement of the trial, and then at regular intervals (at least annually) until completion. The TSC will be chaired by an Independent member and comprise two other independent members, the Grant Applicants (including the lay member), and representatives of the sponsor and funder. The standard University of Nottingham Trial Steering Committee Charter and Contracts will be used.

Specific tasks of the TSC are:

- To approve the trial protocol.
- To approve necessary changes to the protocol based on considerations of feasibility and practicability.
- To receive and review reports from the DMC.
- To resolve problems brought to it by the co-ordinating centre and TMC.
- To lead on publication of the trial results.

Data Monitoring Committee (DMC)
An independent Data Monitoring Committee will be established. The DMC will receive safety reports every six months, or more frequently if requested and perform unmasked reviews of efficacy and safety data. The DMC will perform a formal interim analyses after 400 participants have been recruited and followed-up at 90 days.

The standard University of Nottingham Data Monitoring Committee Charter and Contracts will be used containing details of membership, terms and conditions and full details of stopping guidelines. The DMC will report their assessment to the independent chair of the TSC and the CI. They will not, however, provide specific unmasked results to the TSC or Chief Investigator.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

Participant Duration
Each participant will be in the trial for 365 days. They will have 4 days of treatment and be followed-up at 90 days (primary outcome) and 365 days after randomisation.

Study Duration
The trial is funded for three years at present.

End of the Trial
The trial will end when the final participant has completed the treatment period and 365 day follow up.
There will be two database locks for this trial. The first will be after all day 90 data have been received and checked. Analysis of the primary, secondary and safety end points to this point will then be performed. The second database lock will be after all day 365 data (the longer term follow-up) have been received and checked. Analyses of the long term outcomes will then be performed.

It is planned that the results to 90 days will be presented and published separately from the 365 longer term follow-up data.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

The study will be set both within the ambulance service and in secondary hospital care. The study will recruit and initially treat participants whilst in the care of the ambulance service. The patients will then be transferred to hospital where their treatment and their participation in the study will continue.

Patients will be approached by the paramedic to determine interest and consent for the study. As per normal stroke care, the paramedic is part of the participant's usual care team.

Patients with ultra-acute FAST-positive (2 or more) presumed stroke and systolic BP >=120 mmHg presenting to paramedics in the context of a 999 ambulance call for 'stroke' will be approached to participate in the trial. The paramedic will assess the potential participant for the trial at the scene and/or in the ambulance. The paramedic will then briefly explain the trial using a short pictorial information sheet as reference for the patient and obtain consent for participation in the trial.

Since patients will be approached by paramedics in the ambulance setting, and the first dose of treatment should be given prior to admission to hospital, it will not be possible to use interpreter and translator services.

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Eligibility criteria

Inclusion criteria

- Patients presenting to paramedics in context of 999 ambulance call for 'stroke'.
- Age 18 years or more (there is no maximum age).
- 'Face/Arm/Speech' Time (FAST) score 2 or more
- Onset <=4 hours.
- Systolic BP >=120 mmHg.
- Have provided informed consent, or a relative/paramedic has provided proxy consent
- Paramedic is trained in RIGHT-2 procedures, is from a participating ambulance station, and will take patient to a participating comprehensive/primary stroke centre.

Exclusion criteria

- Patient at a Nursing Home.
- Glucose (BM stix) <2.5 mmol/l.
- Glasgow Coma Scale <8
- Witnessed seizure/fit at presentation.
- Known life expectancy <6 months.

- Known to have taken a PDE5 inhibitor, such as sildenafil, in previous day before stroke.
- Known sensitivity to Transiderm Nitro patch.
- Known sensitivity to Duoderm hydrocolloid dressing.
- Known previous enrolment into RIGHT-2.

Expected duration of participant participation
Study participants will participate in the study for 365 days. They will receive treatment for the first 4 days of the study and be followed up at 90 days (primary outcome) and 365 days from their stroke.

Removal of participants from therapy or assessments
Participation in the trial is voluntary and patients are free to withdraw from the trial at any stage without giving a reason. Study medication may be stopped at any time by the investigators or any treating clinician if deemed in the patient's best interests. Randomised treatment will be given on top of 'best medical care'.

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

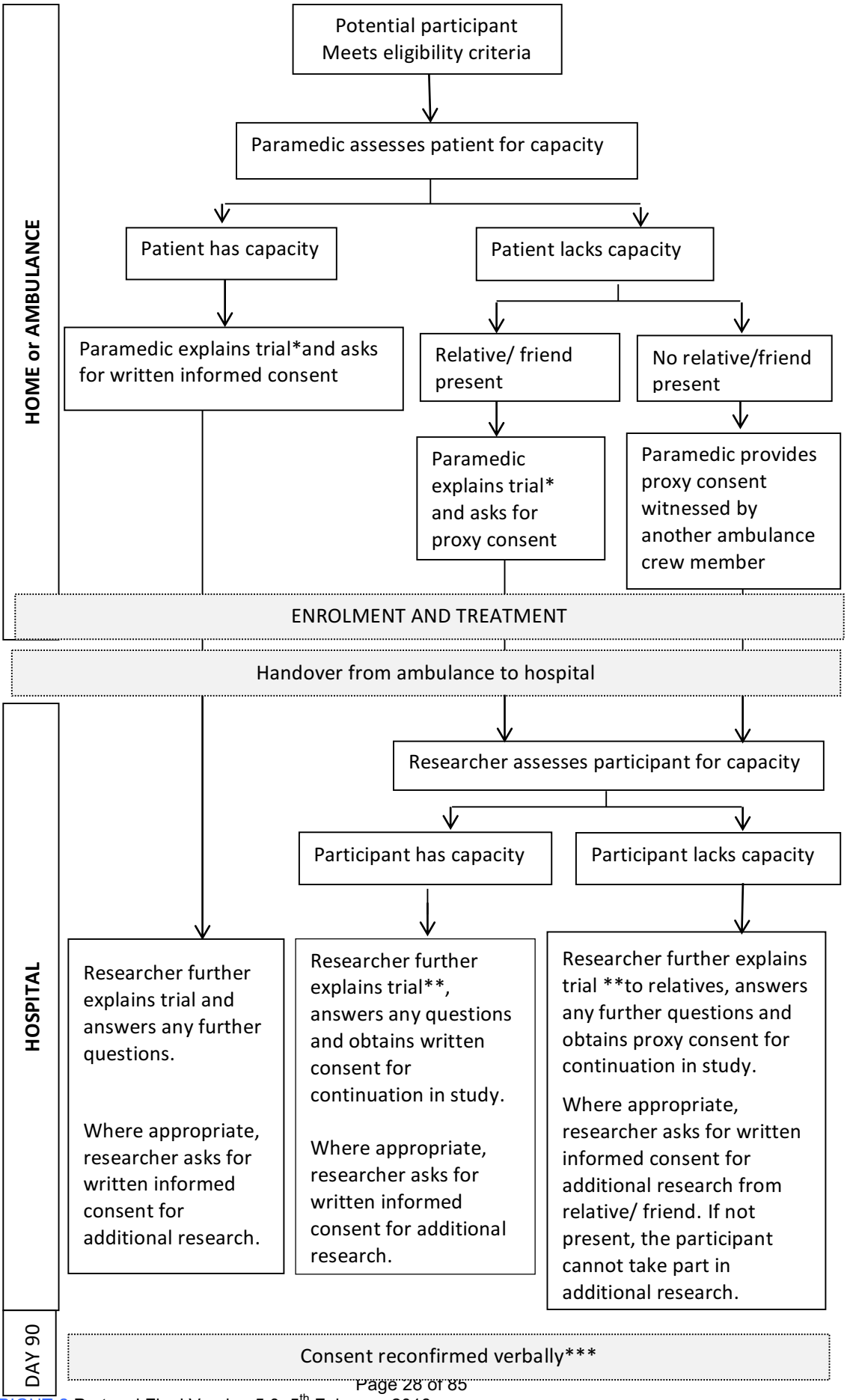
Participants may withdraw from receiving trial treatment but remain in the trial and be followed up.

Where participants are found to not have had a stroke, their treatment should be discontinued and there is no requirement for them to have the 2nd CT scan. They should still be followed up at 90 and 365 days.

Withdrawal from treatment
Participants may withdraw from taking GTN/sham at any point during the 4 days of treatment. Follow-up will continue unless participants also indicate that they wish to withdraw from the whole trial.

Withdrawal from the trial
Participants may withdraw from the trial at any point. They will be asked, but are not required, to provide a reason for withdrawal. If a participant withdraws from the trial, they will not have any further follow-up. All data collected up until that point will be used in analyses.

Informed consent



*Using short information sheet/consent form **Using long information sheet and consent to continue form
***If participant contacted by post, return of questionnaires will represent consent to continue participation in the study

Paramedic consent
In ambulance

Consent for the following will be obtained by the paramedic (including informed, proxy (relative/paramedic) consent):

- 4 days of treatment with GTN/sham patches.
- An additional CT scan on Day 2.
- Being contacted by telephone (or mail) for follow-up at Days 90 (primary outcome) and 365
- Access to the participant's data (medical and other relevant to the trial e.g. change of contact details).

Assessment of capacity
The paramedic will tell the patient that:

- they have had a suspected stroke
- they have higher than ideal blood pressure that needs to be lowered
- they can be in a trial where they will have patches placed on their back for 4 days which will either contain medicine that will lower their blood pressure, or will not contain the medicine.

They will then ask the patients 3 questions to assess their capacity (diagnosis - stroke, problem – blood pressure needs lowering, treatment - patch). If the patient is able to answer the three questions correctly, capacity is assumed.

- If patient has capacity they may give consent.

If the patient does not have capacity, the paramedic will explain the trial to a relative, carer or close friend if they are immediately available. The relative, carer or close friend (able to represent patients views and wishes) may then give legal representative (proxy) consent.

If patient lacks capacity and no relative, carer or close friend is present then the paramedic may give proxy consent, with another ambulance crew member signing as a witness in person.

In hospital
When the ambulance arrives at hospital, the paramedic will hand the treatment pack, completed ambulance CRF, Information Sheets, and Consent Form to the receiving staff. The paramedic will keep carbon copies of the Consent Form and CRF, and file them in a locked cupboard at their ambulance station to be periodically sent back to the co-ordinating centre; these may be used as source data if required.

During their hospital stay, the participant will be approached by a member of the research team as soon as practically possible.
The member of the research team will:

- Provide more detailed information about the study (including a more detailed information sheet) and answer any questions the participant and/or their relative, carer or close friend may have.
- Explain additional research options available and ask for their consent to participate, if appropriate.

Participants with capacity to provide consent for themselves in the ambulance will not be required to provide further consent to continue in the main study. If they wish to take part in the additional research they will be asked to sign a separate consent form.

Where proxy consent was obtained, the participant may be assessed to determine if they now have capacity to consent. If they have regained capacity they will be given a full information sheet detailing the study and will be asked to provide their written informed consent to continue in the study in a separate consent form for study continuation. Re-assessment of capacity in those where proxy consent was obtained can be performed at any point during the trial (e.g. prolonged hospitalisation) and will be conducted using the same method as the paramedic used.

Where a participant still lacks capacity, a relative, carer or friend will be sought to provide legal representative consent to continue participation in the study. They will be given a full information sheet detailing the study and will be asked to provide their written informed consent for the participant to continue in the study on a separate consent form for study continuation.

If the patient is unable or unwilling to write or mark (e.g. in the presence of dominant hand weakness, ataxia or dyspraxia), witnessed verbal consent may be recorded on the consent form. Alternatively, proxy consent may be obtained from relatives or carers if the patient is unable to give meaningful consent (e.g. in cases of dysphasia, confusion, or reduced conscious level). These approaches are standard practice in acute stroke trials. Where the patient is unable, lacks capacity and no relative/carer/friend is present, the paramedic may give consent, as done in the RIGHT trial.

Consent for additional research

The following additional research may be performed in some centres as part of the trial.

- Ambulatory Blood Pressure Monitoring research – the patient would wear an ambulatory blood pressure monitor for 24 hours starting as soon as possible after admission to hospital.
- Transcranial Doppler (TCD) research – TCD would be performed as soon as possible after admission, up to and including day 3.
- Pulse wave analysis (PWA) research – central systemic blood pressure and augmentation index would be measured as soon as possible after admission, up to and including day 3.
- Blood biomarker research – blood samples for future testing would be taken on Days 1, 2 or 3, centrifuged and the supernatant stored frozen at -20 degrees C or lower (ideally -70/-80 degrees C). P-selectin research – a blood sample for future testing would be taken on Days 1, 2 or 3.
- Genetic research - a blood sample for future testing would be taken during their hospital stay. The sample would have DNA extracted and be stored frozen at -20 degrees C or lower (ideally -70/-80 degrees C).
- Qualitative data from patients within the East Midlands discharged to the community and EMAS NHS Trust Paramedics involved in the trial will be sought to explore their experiences and perspectives of participation with a specific focus on ethical issues such as consent (Appendix L).
- Qualitative data from Paramedics involved within participating ambulance trusts will be sought explore the experiences of participation in ambulance-based trials to inform the objectives detailed in Appendix M

Not all research will be available in all centres and participation in these is not mandatory. A separate information sheet detailing the additional research will be provided and written informed consent will be required for participation using a separate consent form specifically for the additional research.

The measurements would be taken using the equipment already available in the centre. No central calibration would be required.

The participant will be reassured that their participation is optional and that their care will not be compromised whatever their decision. They will also be reassured that they can continue in the main trial without having to take part in any additional research.

- If patient lacks capacity then a relative, carer or friend may give proxy consent, for the additional research if immediately available. The relative/carer/friend will be given a separate information sheet and consent form specific to the additional research.
- If patient lacks capacity and no relative/friend is present then the patient will remain in the main trial but no additional research will be possible.

Co-enrolment in other trials

Concurrent uncoordinated co-enrolment of patients into two or more randomised controlled trials has the potential for confounding, e.g. when the treatments have a similar mechanism of action, or when adverse events could interact, or when similar outcomes are being measured. Patients should not be enrolled into RIGHT-2 if they are known to be already in another drug, device or biological intervention trial. Equally, once in RIGHT-2, a patient should not be enrolled into another randomised trial involving a drug, device, or biological intervention until final follow-up has occurred. Patients may be co-enrolled into non-intervention trials and rehabilitation studies providing these do not involve a drug, device, or biological intervention.

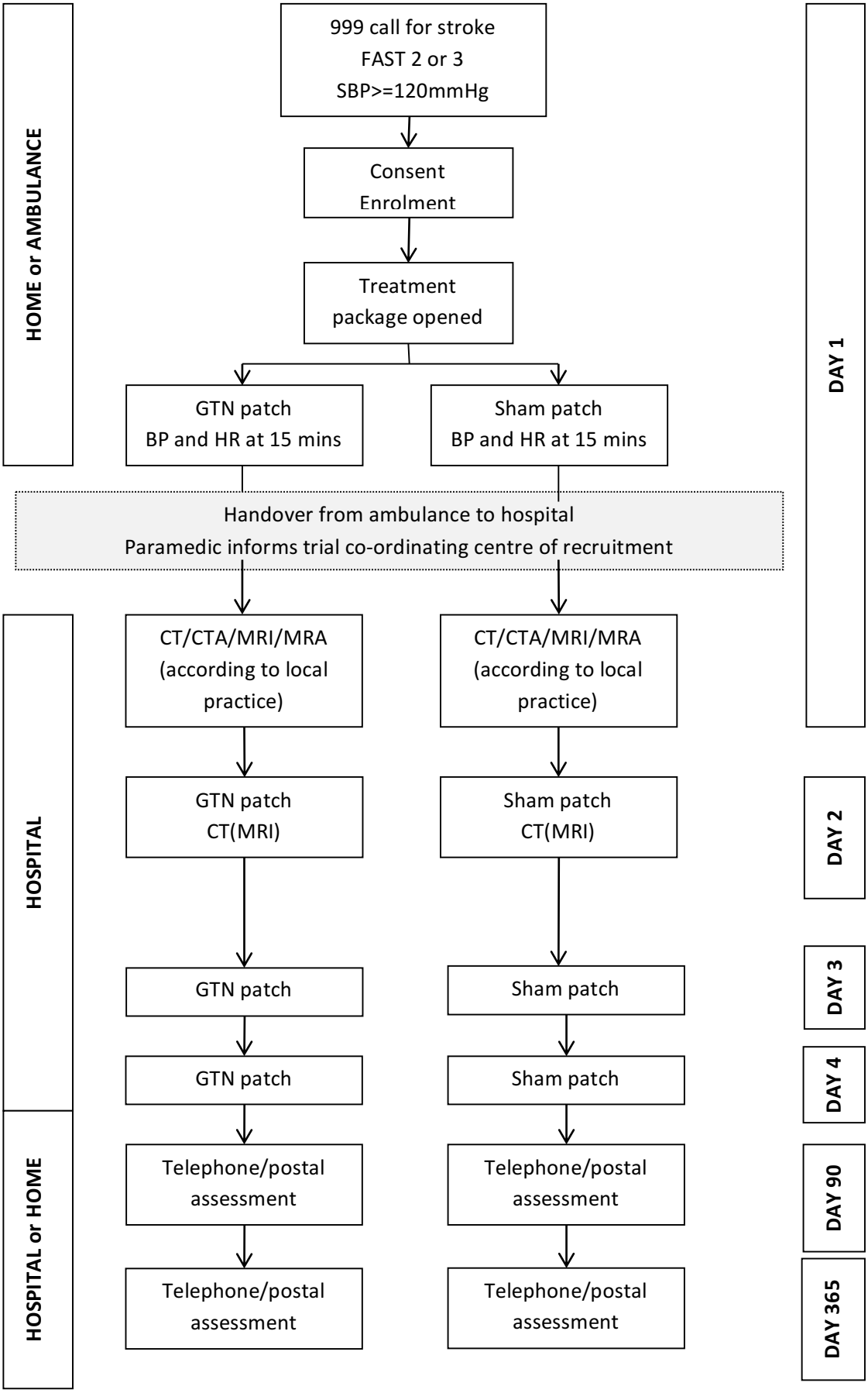
TRIAL / STUDY TREATMENT AND REGIMEN

Trial treatment: After consent, the paramedic will open the pack randomly assigned to that ambulance. Randomisation will be equal (1:1 GTN : sham). They will put the treatment, i.e. either GTN or sham patch, onto the participant's shoulder or back. This will then be covered with gauze to reduce the chance of the participant knowing what treatment they have been randomised to. The paramedic will leave a message on a dedicated answerphone accessed only by staff involved in the study at the Coordinating Centre in Nottingham with information on the randomisation (eg paramedic name, ambulance station, hospital name, patient initials, treatment pack number, date and time of randomisation) and receiving hospital. BP and heart rate will be measured at 15 minutes, or immediately before arrival at hospital if earlier. The participant may be given a wristband to show that they are in the trial.

Once in hospital, the participant will be approached by a member of the research team who will answer any further questions they may have.

Daily GTN/sham patches should be continued in hospital for a further 3 days. These should be administered at 8am (+/- 2 hours) on Days 2, 3 and 4.

All other best medical care treatments will be used according to local protocol.



If proxy consent has been given prior to study start, the participant should have their capacity reassessed in hospital. If they have regained capacity, they should be asked to provide written consent to continue in the study. If they have not regained capacity, written consent to continue in the study should be sought from a relative or friend. Full information sheets will be provided to aid in the participant's (or relative/friend's) decision making.

Participants will be assessed (history, examination, investigations, initial diagnosis, initial treatment) as normal, e.g. in the Accident & Emergency Department (A&E/ED) or on the Hyper-acute/Acute Stroke Unit according to normal practice. All patients will receive a diagnostic CT scan as soon as possible after admission as part of normal practice. A CTA and/or CTP will also be done if part of routine practice but is not a mandatory part of the research protocol. MRI (e.g. T2, DWI and a blood-sensitive sequence - T2*, GRE or SWI) and MRA may be used instead of CT if part of normal practice.

It is expected that participants will receive best medical care in hospital. Where ICH has been excluded thrombolysis should be administered as soon as possible, if appropriate. If undertaken as part of routine care, mechanical thrombectomy may also be performed if clinically indicated. Hemicraniectomy may also be performed as required. Aspirin and/or other antiplatelet agents should be commenced in IS. BP may be lowered to <185 mmHg prior to thrombolysis according to local guidelines. Where ICH is shown on brain scanning, BP may be lowered according to local practice. Patients in A&E/ED should be moved to the Hyper-acute Stroke Unit as soon as reasonably possibly.

On Day 2 (up to and including day 4) a head scan will be performed for all participants. This is not always routine for stroke patients. This head scan would usually be CT (or MRI if clinically indicated).

Depending on which centre a participant is being treated and when the researcher is able to discuss the study with them, written informed consent may be sought for additional research samples or assessments.

These additional assessments/samples would be taken as follows:
Days 1, 2 or 3: 24 hour ambulatory blood pressure monitoring (as soon as possible)
Days 1, 2 or 3: Transcranial Doppler measurement (as soon as possible)
Days 1, 2 or 3: Pulse wave analysis (as soon as possible)
Days 1, 2 or 3: Blood samples for biomarker measurement (20ml)
During the participant's hospital stay: Blood sample for genetic testing (5ml)

Perform 24 hour ambulatory blood pressure monitoring as soon as possible. TCD and PWA to follow if available.

Day 30 onwards or following discharge whichever is earlier: Interviews up to 1 hour with patients from the East Midlands region (Appendix L).

Paramedics participating in the trial from the East Midlands Ambulance Service NHS Trust will be interviewed who have completed the trial training (Appendix L).

Participants will be followed up by telephone (or post if unavailable by telephone) 3 months and 1 year after their stroke. Their mortality status will be checked prior to contact using either their GP or the Health and Social Care Information Centre and consent for continued participation verbally confirmed prior to outcome measurement.

They will be asked to respond to various questions from validated questionnaires assessing dependency (Modified Rankin Scale), disability/activities of daily living (Barthel Index), Quality of Life (Health Utility Status derived from EQ-5D and the EQ-VAS), cognition (Adult lifestyles and function interview (ALFI) - MMSE, Telephone Interview Cognition Scale (TICS), animal naming – these would be amended for postal questionnaires), mood (Zung Depression Scale), patient disposition and stroke recurrence.

If the participant lacks capacity or is unable to answer some questions, a relative/friend/carer may respond on the participant's behalf. If questionnaires are sent by post, the return of the questionnaires will represent consent to continued participation in the study.

Paramedics who express interest in participating in the qualitative research study exploring research activity in ambulance services will be interviewed during the recruitment phase of the main trial (Appendix M).

Table 7. Flow of participants

	Baseline Day 1	+15 min	Day 1	Day 2	Day 3	Day 4±1	Discharge	Discharge	Day 90±7	Day 365±7
Environment	Amb	Amb	Hospital admission	Hosp	Hosp	Hosp	Hosp	Home / Community	Tel/post	Tel/post
Paramedic: Consent/proxy-consent for main trial	✓									
Enrolment	✓									
Baseline assessment: FAST, BP/HR, ECG	✓									
Administer GTN/sham + gauze dressing	✓			✓	✓	✓				
Blood pressure & heart rate		✓	✓	✓*	✓*	✓*				
Paramedic-hospital handover			✓							
Consent if patient lacks capacity in ambulance~			<	=	=	=	>			
Impairment / deterioration (NIHSS/GCS)			✓	✓	✓	✓				
CT brain, plain †			✓	<	=	>				
CT angiography - if routine †			✓							
Haematology/chemistry/ECG - routine			✓							
All SAEs including fatal SAEs			✓	✓	✓	✓	✓**			
Fatal SAEs							✓		✓	✓
Recurrent stroke			✓	✓	✓	✓	✓		✓	✓
Tolerability/side effects			✓	✓	✓	✓				
Plain CT scan - *routine if post rt-PA †*				<	=	>				
Additional clinical neuroimaging			✓	✓	✓	✓	✓			
Consent for additional research (where appropriate)			✓	✓	✓					
24 hour ambulatory blood pressure monitoring ‡			<	=	>					
Blood biomarkers (e.g. S-100/NOx/P-selectin) ‡			<	=	>					
Genetics: EDTA sample (optional – one sample) ‡			<	=	=	=	>			
,Pulse Wave Analysis ‡			<	=	>					
Transcranial Doppler ‡			<	=	>					
Consent if patient regains capacity			<	=	=	=	>			
Disposition (home/institution/home)							✓		✓	✓
Dependency: modified Rankin Scale									✓	✓
Disability: Barthel Index									✓	✓
Cognition: MMSE, TICS									✓	✓
Quality of Life: EQ-5D, EQ-VAS									✓	✓
Mood: Zung Depression Scale									✓	✓
Semi-Structured Interview (East Midlands only)								✓		

*1-2 hours after administration of GTN/sham patch; **If discharge before Day 4; *Routine care in italics.* ‡Additional research. Amb: Ambulance; BP: Blood pressure; FAST: Face, Arm, Speech, Time test; GCS: Glasgow Coma Scale; Hosp: Hospital; HR: heart rate; IMP: Investigational Medicinal Product; MMSE: Mini-Mental State Examination; NIHSS: National Institutes of Health Stroke Scale; Tel: Telephone (done by central telephone questionnaire masked to treatment assignment); TICS: Telephone Interview of Cognition Status. † Imaging sent as 'volume data'‡ Separate consent to be obtained in-hospital. 08.00 Time (+/- 2 hour) for patch administration or measurement ~Only for participants whose baseline consent was by proxy. Can be anytime over hospital stay.

GTN/sham patch management
Four daily doses of GTN/sham patches will be administered with the first in the ambulance and the remaining three in hospital, unless:

- If a patient is diagnosed with a TIA or stroke mimic (e.g. infection, fit, tumour) treatment will be withdrawn once the new diagnosis is made; the number of patches administered and final diagnosis will be recorded in the eCRF.
- If a patient has a minor stroke and is suitable for discharge home before the end of treatment, treatment will be withdrawn; the number of patches administered and final diagnosis will be recorded in the eCRF

The patches should be administered at 8am (+/- 2 hours) starting the day after the stroke/administration of the first patch.

Concomitant Treatments
Antihypertensive drugs taken before the stroke should not be re-started immediately; instead they should be recommenced once the patient is stable and enteral access has been obtained through oral feeding or insertion of a nasogastric tube.[26]

Clinical hypotension during treatment
If symptomatic falls in blood pressure occur, e.g. with 'faintness' or neurological deterioration, a stepped approach to management may be practiced (as done in ENOS [26]):

- Monitor closely.
- Raise the patient's legs.
- Administer intravenous saline or colloid.
- Remove GTN/sham patch.

Following adequate hydration it should be possible to restart patch therapy on the next day in most cases.

Severe hypertension during treatment
If severe and sustained hypertension (systolic blood pressure > 220 mmHg) develops during the treatment phase of the trial, a stepped approach to management may be practiced (as done in ENOS [26]):

- Monitor closely.
- Continue the randomised treatment.
- Treat with open label glyceryl trinitrate (patch, paste or intravenous), or labetalol.

Compliance
Compliance will be assessed by examining the record of treatment administration on the eCRF. Participants should have received one GTN/sham patch for each of 4 consecutive days. From the perspective of per protocol analyses, sufficient treatment will be deemed to have occurred if the first 2 patches are received.

Accountability for GTN patches & sham patches
Logs should document the following movement of treatment packs:

- Transfer from NUH Pharmacy to Ambulance Service central Pharmacies.
- Transfer from Ambulance Service central Pharmacies to Ambulance Stations.
- Transfer from Ambulance Station to Ambulance at start of paramedic shift.
- Transfer from Ambulance to Ambulance Station at end of paramedic shift if pack not used.
- Transfer from Ambulance to Hospital if pack used.
- Treatment in hospital.

On completion of the study, or if unused packs are required at other Ambulance Stations, further logs will document the movement of treatment packs:

- Transfer from Ambulance Station Service central Pharmacy to NUH pharmacy.
- Receipt and disposal of unused packs at end of trial.

Management of study drug overdose
Unless multiple GTN patches are used in parallel, overdose is unlikely to occur. If significant treatment related adverse events occur, e.g. headache or symptomatic hypotension, the GTN patch/sham patch may be removed. Dehydration/hypovolaemia should be treated in the presence of hypotension.

Criteria for terminating trial
The trial may be terminated by either the TSC, the sponsor or the funders as a result of a formal or informal interim analysis and based on overwhelming evidence of significant safety concerns, major efficacy, new information, or issues with trial conduct (e.g. poor recruitment, loss of resources). Any decision to stop the study prematurely will be based on asymmetric stopping rules.

The trial may be stopped at individual sites due to unacceptable performance in recruitment and/or failure to comply with protocol.

RADIATION EXPOSURE
Details of diagnostic or therapeutic ionising radiation
The participant will receive a routine clinical non-contrast single run CT head scan at the time of presentation with stroke; where routinely done, a CT angiogram of the head will also be done. The CT head scan(s) done at the time of admission to hospital is part of routine clinical care. The results will be used as baseline data. An additional non-contrast single run CT head scan will be done on day 2; this is routine after thrombolysis.

Trial Procedures
Single run non-contrast CT (or MRI if clinically warranted) head scan 1 day post recruitment (day 2, up to and including day 4). CTA/MRI/MRA brain may be used if clinically warranted, the correct sequences are performed, and an image test series passed quality control assessment during start up.

Details of radioactive materials and dose
Using the DLP's recorded in the latest CT dose survey for CT Head [Acute Stroke] of approximately 1000 mGy.cm and the previous NRPB effective dose co-efficient of 0.002 mSv/mGy.cm one arrives at an effective dose from such a scan of 2 mSv.

This gives a total protocol dose of approximately 4 mSv with 2 mSv of this being additional to standard of care.

It is possible that an upper bound of three times this mean survey dose could be delivered by some centres leading to a maximum protocol dose of 12 mSv [again with 50% additional to standard of care].

These doses should be compared with the annual average UK radiation dose from background radiation of approximately 2 mSv, which is about the same as the additional dose from this study.

Clinical Assessment
Assuming a normal life expectancy and using the ICRP103 detriment adjusted nominal risk coefficient for cancer of 4.1%/Sv we get an approximate risk of harm from cancer induction of 1 in 6,000. The additional risk is approximately one half of this. If centres are at the higher

end of the dose spectrum then all these risks will be approximately tripled with a concomitant change in the relation to natural risks.

This should be compared with the natural risk of cancer induction of greater than 1 in 3 [i.e. 2,000 times higher than the additional risk posed by this study]. It is about the same risk as that of dying in a motor accident from 3 years driving.

Public Health England deem this risk from the additional CT x-ray examination to be 'very low risk'.

Neuroimaging
The CT scan itself takes about a minute and does not involve any injections. The scan uses x-rays, which in large amounts can be harmful, but for this extra CT head scan the additional risk to the participant from the scan has been judged to be extremely small.

The objective of the exposure is to assess the extent of the stroke (infarction due to blood clot, or haematoma due to bleeding) in the brain to see if it has got larger or stayed the same size following treatment. It will also show if signs of arterial occlusion on the admission scan have disappeared, or if there is swelling in the infarct/haemorrhage, or secondary bleeding into the infarct.

An alternative would be MRI brain scan but this takes longer and some patients are unsuitable or unable to tolerate it due to claustrophobia. Further, MRI is often not available in emergency situations or out of working hours.

The procedure for CT and any doses in lay terms are explained in the participant information sheet.

TRANSPORT AND STORAGE OF THE TISSUES

Optional blood samples for further research will be taken in some centres subject to additional consent.

Genetic research - a blood sample for future testing would be taken during the participant's hospital stay. The sample would have DNA extracted and would be anonymised and stored frozen at -20 degrees C or lower (ideally -70/-80 degrees C). Analyses would be based on the latest research findings. At the end of the study, these samples would be retained indefinitely.

Blood biomarker research – blood samples for future testing would be taken on Days 1, 2 or 3, centrifuged and the supernatant stored frozen at -20 degrees C or lower (ideally -70/-80 degrees C). Biomarkers of interest, including S100 [46] and NOx [19] [35], will be identified and analysed. When the analyses are complete, the samples will be destroyed.

Samples will be stored in linked anonymised format at the University of Nottingham and labelled using a combination of date of birth, initials and study number to permit accurate linkage to clinical data and the consent form in accordance with the Human Tissue Authority Code of Practice. Further details will be available in the data management plan.

The analysis of samples will take place at the University of Nottingham within Stroke, Division of Clinical Neurosciences. All shipments will contain a complete inventory of all samples, along with the name of the person responsible for sending the samples. Once

analysis has taken place, samples will be transported back to the University of Nottingham and stored within the Research Tissue Bank for future research (DI Dr William Dunn - Licence Number 12265) if participants are agreeable and sign the optional clause on the consent form.

Where participants do not agree to the future use of the samples they will be destroyed in accordance with the Human Tissue Act, 2004.

Further details of the preparation, transportation, storage and labelling of these samples will be provided in the trial manual.

LABORATORY ANALYSES

Analyses of the blood samples will be performed at the University of Nottingham and will be further described in the laboratory manual.

Genetic research – a 5ml EDTA blood sample for future testing would be taken during the participant's hospital stay. The sample would have DNA extracted and would be anonymised and stored frozen at -20 degrees C or lower (ideally -70/-80 degrees C). Analyses would be based on the latest research findings. At the end of the study, these samples would be retained indefinitely.

Blood biomarker research – a 7ml clotted blood sample (serum) and 4ml EDTA blood sample (plasma) for future testing would be taken on Days 1, 2 or 3, centrifuged and the supernatant stored frozen at -20 degrees C or lower (ideally -70/-80 degrees C). Biomarkers of interest including S100 and NOx would be identified and analysed. When the analyses are complete, the samples would be destroyed.

P-selectin research – a 4ml citrate blood sample would be taken on Days 1, 2 or 3, fixed (to allow batching of samples), posted to Nottingham using pre-purchased blood sample containers and P-selectin measured using a standardised assay[47].The analyses will be conducted at Stroke, Division of Clinical Neurosciences, University of Nottingham. All measurements are performed by flow cytometry and are subject to strict quality control.

All tests will be performed on anonymised samples and participants will not be informed of the results.

STATISTICS

Methods

The analysis and reporting of the trial will be in accordance with CONSORT guidelines. A full statistical analysis plan will be developed and published prior to completion of data collection.

Continuous variables will be summarised as the mean (standard deviation) and number of observations; ordered categorical data variables will be summarised as the median, lower and upper quartiles, minimum, maximum and number of observations. Binary variables will be summarised in terms of frequency counts and percentages. Descriptive statistics of demographic and clinical measures will be used to compare balance between the randomised arms at baseline. Analyses will be performed using the SAS and/or SPSS statistical packages.

Where patients die before an assessment, a worst score will be assigned,[26] as is already done for modified Rankin Scale, Health Utility Status and Barthel Index:

- 100: Length of stay in hospital if died in hospital.
- 43: National Institutes of Health Stroke Scale (NIHSS).
- 6: modified Rankin Scale (mRS).
- 0: Health Utility Status (HUS).
- -1: telephone-Mini-Mental State Examination (tMMSE), Telephone Interview Cognition Scale (TICS), EuroQoL-Visual Analogue Scale (EQ-VAS), animal naming.
- -5: Barthel Index (BI).

Sample size and justification

The null hypothesis (H_0) is that GTN will not shift the mRS in participants with ultra-acute stroke. The alternative hypothesis (H_1) is that mRS will shift between those stroke participants randomised to GTN versus sham.

A total sample size of 1300 participants (650 in each arm) is required to detect a shift in mRS with an odds ratio of 0.70 (equivalent to a binary odds ratio of 0.66). This assumes an overall significance level of 5%, and 90% power. This calculation assumes a distribution of mRS scores as shown in table 8.

Table 8. Distribution of mRS from [22]

mRS (%)[22]						
0	1	2	3	4	5	Dead
2%	17%	20%	15%	10%	12%	24%

The calculation also assumes 3% loss to follow-up, and reduction for baseline co-variate adjustment of 20% and a non-stroke proportion of 34%.

If only 650 participants are randomised to the trial, there will be 82% power to detect this odds ratio using the same assumptions above. The sample size calculation is relatively insensitive to variations in the mRS.

Whilst one formal interim analysis is planned, no adjustment has been made to the sample size given the pre-specified high level of significance required to stop the trial.

Assessment of efficacy

Primary end point analysis

The shift in mRS between treatment groups will be examined using ordinal logistic regression (OLR) with adjustment for prognostic baseline covariates:

- Age, sex, pre-morbid mRS, FAST, pre-treatment systolic BP, index event (ICH, ischaemic stroke, TIA, mimic), time to treatment administration.

The assumption of proportional odds will be tested using the likelihood ratio test. Multiple linear regression, with covariate adjustment, will be used if the assumption fails.

Primary end point sub-group analysis
Comparison of the effect of GTN vs. no GTN on the primary outcome will be performed in the following pre-specified subgroups (assuming sufficient numbers in each sub-group) with assessment of interaction between treatment, mRS and:

Pre-morbid or pre-randomisation ambulance-determined information

- Age (<80, >=80 yrs)
- Sex (female, male)
- History of treated hypertension (no, yes)
- History or previous stroke (no, yes)
- Pre-morbid mRS (0, 1/2, >2)
- Time to treatment (<1, 1-1.9, >=2 hr)
- Glasgow Coma Scale (15, 12-14, <12)
- FAST score (2, >2)
- Baseline systolic BP (<140, 140-179, >=180 mmHg)

Post-treatment hospital-determined information

- Stroke clinical syndrome (LACS, POCS, PACS, TACS [48])
- Stroke severity (NIHSS <8, 9-12, >12)
- Index event (non-stroke, TIA, IS, ICH)
- Patho-aetiology (IS: SVD, CE, LAD, mixed, other; ICH: basal ganglia, cortical)
- Reperfusion treatment (mechanical thrombectomy, intravenous thrombolysis only, none)
- Brain frailty on neuroimaging (none, some present, all factors present)
- Small vessel disease on neuroimaging (none, mild-moderate, severe)

These analyses are exploratory and not powered for prospective statistical analysis. The hospital-determined information is presented separately since their event rates may be modulated by prior paramedic-delivered GTN treatment, if effective, e.g. conversion of TACS to PACS; reduction in neurological impairment (NIHSS); conversion of ischaemic stroke to TIA; need for reperfusion therapy.

Secondary end point and safety analyses
The following analysis methods will be used to examine the secondary end points. All secondary analyses will be considered supportive to the primary analysis and will be based on the ITT population.[26]

- Continuous data with analysis by multiple regression: HUS, EQ-VAS, MMSE, TICS, ZDS, AI, CBP.
- Continuous data with analysis by repeated measure ANOVA: Blood pressure, heart rate, and their derivatives.
- Ordered categorical data with analysis by ordinal logistic regression: Adverse event by severity (fatal/serious non-fatal/pre-specified adverse events/none [49]), arterial patency on CTA, thrombus burden, collateral scores, tissue perfusion deficit and infarct or haematoma size.
- Time to event binary data with analysis by Cox Regression and Kaplan-Meier: Death, all SAEs.
- Binary data with analysis by binary logistic regression: Headache, hypotension, recurrence, need for hemicraniectomy.

Neuroimaging adjudication
Brain plain CT, CTA and CTP (or MR/MRA) data will be adjudicated for infarcts (presence, depth of ischaemia, size, location, ASPECTS score), haemorrhages, pre-stroke structural brain changes (old infarcts, atrophy, white matter disease) according to methods established and validated for IST-3 and ENOS,[26, 50] and CTA methods used in other trials (IST-3, DIAS-3, DIAS-4, IMS-3, EPITHET, tenecteplase), including: score for the site, and degree of obstruction of any large artery (ICA, MCA, PCA, ACA, BA, VA), arterial patency in the arterial territory distal to the thrombus, thrombus burden, adequacy of collateral pathways, and extent of any visible tissue perfusion deficit (TIMI, IST-3 score).[50-53] ICH will be adjudicated for haematoma size (in all) and spot sign (in those with CTA),[26, 54] the former if CT has been done. Scoring will be performed blind to all data on a high definition workstation by a neuroimaging expert trained in angiography interpretation. Exemplar scoring sheets are available at www.bric.ed.ac.uk/research/imageanalysis.html#ais.

Procedures for missing, unused and spurious data
Imputation of missing data will not be performed.[26] The primary analysis will be performed on all randomised patients with a valid mRS score at 90 days.

Definition of populations analysed

The following populations definitions will be used:

1. ITT: Primary Safety analysis - All randomised patients with vital status recorded at day 90.
2. ITT: Primary Efficacy analysis - All randomised patients who received at least one GTN/sham patch and with a valid mRS recorded at day 90.
3. Modified ITT 1: Sensitivity Efficacy analysis - As in 2 but limited to patients with a diagnosis of stroke, i.e. no TIA or mimics.[22]
4. Modified ITT 2: Sensitivity Efficacy analysis - As in 2 but limited to patients with a diagnosis of stroke or TIA, i.e. no mimics.
5. PP: As in 3 but limited to stroke patients who fulfilled all key inclusion criteria, i.e. recruitment <4 hours, FAST 2 or 3, systolic SBP >=120 mmHg, and not from a nursing home.

Protocol violations

The following will be considered to be violations of the protocol:
Ambulance:

- Failure to obtain consent
- No witnessed signature for proxy consent
- Randomisation over 4 hours from onset of symptoms
- FAST score of 0 or 1
- Systolic blood pressure less than 120 mmHg
- Glasgow Coma Scale less than 8
- Glucose less than 2.5 mmol/L
- Patient from nursing home
- Patient did not receive first GTN/sham patch
- Already in another trial
- Hospital not informed of trial participant
- No message left on trial phone (notification of new participant)

Hospital

- Failure to enter ambulance baseline data sheet
- Failure to enter hospital admission form
- Failure to obtain consent where applicable
- Participant does not receive all of the randomised treatment as per protocol
- Failure to enter day 4 follow-up form
- Failure to enter discharge/death form
- Subsequent randomisation into another trial
- Failure to report/submit SAEs

Follow-up

- Day 90 follow-up performed before day 83 or after day 104
- Day 365 follow-up performed before day 345 or after day 385

Miscellaneous

- Any other major deviation from the trial protocol

ADVERSE EVENTS

Definitions

Adverse event
An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.

An AE includes a / an:

1. Exacerbation of a pre-existing illness.
2. Increase in frequency or intensity of a pre-existing episodic event or condition.
3. Condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.
4. Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

An AE does not include a / an:

1. Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.
2. Pre-existing disease or conditions present or detected at the start of the study that did not worsen.
3. Situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).
4. Disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.
5. Overdose of concurrent medication without any signs or symptoms.

Known adverse events associated with GTN are listed in the SmPC. Known stroke SAEs are listed in Appendix H. All AEs will not be collected in RIGHT-2 since GTN has been available for several decades, and has been assessed in large trials in both stroke (ENOS [26]) and non-stroke conditions (GISSI-3 [55]). However, certain known AEs or AEs with relevance to stroke will be collected prospectively as secondary outcomes, in particular headache and hypotension.[26]

Serious adverse event

A Serious Adverse Event (SAE) is any adverse event occurring following study-mandated procedures, having received the IMP or placebo/sham that results in any of the following outcomes:

1. Death.
2. A life-threatening adverse event.
3. Inpatient hospitalisation or prolongation of existing hospitalisation.
4. A disability / incapacity.
5. A congenital anomaly in the offspring of a participant.

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardise the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All adverse events recorded will be assessed for seriousness, expectedness and causality. A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.** This will be counted as "unrelated" for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and

is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

An AE whose causal relationship to the study IMP is assessed by the Chief Investigator as "possible", "probable", or "definite" is an Adverse Drug Reaction

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

All SAEs occurring to the treatment period (up to day 4) will be recorded and reported; after day 4 and up to final follow-up only fatal SAEs will be recorded and reported. Again this reflects the considerable knowledge already known about GTN, including in patients with recent stroke.

Data on stroke recurrence and acute coronary syndrome termed safety outcome events, will be collected up to day 90.

Reporting of adverse events

Where participants have been discharged from hospital, they will be asked to contact the study site immediately in the event of any serious adverse event. All serious adverse events from baseline to Day 4 will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause. Only fatal SAEs will be followed up from Day 5. Where a patient dies and no SAE is submitted, the study site will be approached to determine further information. The Chief Investigator (delegated responsibility by the Sponsor) shall be informed immediately (within 24 hours) of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners.

In the event of a pregnancy occurring in a trial participant or the partner of a trial participant no specific monitoring shall occur during the pregnancy and after delivery to ascertain any trial related adverse events in the mother or the offspring since the study drug is not contraindicated in pregnancy and has shown no teratogenic potential in animal species studied.

All serious adverse events occurring to end of treatment will be recorded and reported to the MHRA and REC as part of the annual Development Safety Update Reports. SUSARs will be reported within the statutory timeframes to the MHRA and REC as stated below. The Sponsor shall ultimately be responsible for adverse event reporting.

SUSARs

A serious adverse event that is either sudden in its onset, unexpected in its severity and seriousness or not a known side effect of the IMP *and* related or suspected to be related to the IMP is classed as Suspected Unexpected Serious Adverse Reaction and requires expedited reporting as per the clinical trials regulations.

All serious adverse events that fall or are suspected to fall within these criteria shall be treated as a SUSAR until deemed otherwise.

The event shall be reported immediately (within 24 hours) of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the study IMP
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action
- If the event is deemed a SUSAR, shall, within seven days, enter the required data on the MHRA's eSUSAR web site.
- Shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event
- Shall, within a further eight days send any follow-up information and reports to the MHRA and REC.
- Make any amendments as required to the study protocol and inform the ethics and regulatory authorities as required

Trial Treatment Related SAEs

A serious adverse event that is unexpected in its severity and seriousness *and* deemed directly related to or suspected to be related to the trial treatment but not the IMP shall be reported to the ethics committee that gave a favourable opinion as stated below.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed related to the trial treatment shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event.
- Shall, within a further eight days send any follow-up information and reports to the REC.
- Make any amendments as required to the study protocol and inform the REC as required

Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study or study treatment at the discretion of the Investigator. They may remain in the trial for follow-up.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be implemented until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be instituted immediately providing that the MHRA, R&D and REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent or relative or paramedic consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant or other legally authorised representative shall both sign and date the Consent Form before the person can participate in the study.

Consent will be obtained in the ambulance for all main trial processes, including ambulance, hospital and follow-up trial activities. Using a single-page information sheet, potential patients will be approached by a trial-trained paramedic to take part in the study in accordance with GCP. Capacity will assessed by ensuring the patient understands their diagnosis (likely stroke), that their blood pressure is higher than ideal, and treatment involves a patch (GTN or sham), a process used in PIL-FAST and RIGHT.[21, 22, 39] If the patient agrees to take part in the study, written consent will then be obtained. For patients lacking capacity (e.g. due to dysphasia, confusion, reduced level of consciousness), a relative or close friend, if present, will be approached to provide proxy consent. If the patient is unable to provide consent and there is no relative present, paramedics will give proxy consent in the presence of a witness, another member of the ambulance crew.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

Consent for additional research procedures and samples will be sought in hospital by a member of the research team.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasise to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Drug accountability

Treatment packs, including GTN patches or sham patches, will be dispensed from pharmacy to each participating Ambulance Station at the start of the trial and then again as needed. Treatment packs will be kept securely in the Ambulance Station.

The Ambulance Service Principal Investigator and Pharmacist shall maintain records of the study drug's delivery to the pharmacy, movement to Ambulance Stations, distribution to each ambulance and participant, and the return to the ambulance station, pharmacy or alternative disposition of unused study drugs. These records will include dates, quantities received, batch / serial numbers, expiration dates, and the unique code numbers (patient trial number) assigned to the trial participant. Investigators and /or the local site pharmacists will maintain records that document adequately that the participants were provided with the correct study medication. These records will be part of each patient's Case Report Form (CRF). All study medication packs received by the pharmacy shall be accounted for.

Case Report Forms

Each participant will be assigned a trial treatment pack ID at enrolment and this number will be entered onto a paper CRF (present in the treatment pack). Once the ambulance baseline data sheet eCRF is entered on-line, a trial number will be generated (in sequence). The ambulance station number, centre number, trial number and participant initials will then be used to form an identifier used on subsequent eCRFs, other trial documents and the electronic database. The participant's initials will be taken from their first and last names separated by a hyphen, or a middle name initial when available. The date of birth (dd/mm/yyyy) is entered into the database once for the use of data verification and is not visible when entering study data

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial in accordance with regulatory requirements and for follow-up as required. Access to CRFs and eCRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out, but not obliterated by using correction fluid, and the correction inserted, initialled and dated.

The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and pharmacy records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall be made available at all times for review by the Chief Investigator or designate, Sponsor's designee and inspection by relevant regulatory authorities (MHRA).

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF/eCRF will only collect the minimum required information for the purposes of the trial. Paper CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers, passwords and PIN (encrypted using a one way encryption method). Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

Imaging data identified by initials, trial number and centre number will be transferred between the trial centre in Nottingham and the Brain Research Imaging Centre in Edinburgh using an authenticated, encrypted connection.

Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham, as research Sponsor, indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; drug accountability, pharmacy records and equipment calibration logs.

The Trial Co-ordinator or delegate such as the National Paramedic and regional Paramedic Champions, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit of Ambulance Services and Ambulance Stations on at least two occasions (start-up and during recruitment) and an audit report shall be made to the Trial Steering Committee. Similarly, the Trial Coordinator, or designee, shall carry out a systems audit of hospital sites on at least two occasions (start-up and during recruitment) and an audit report shall be made to the Trial Steering Committee.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the trial risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

Study results will be published in peer-reviewed journals and presented at local, national or international scientific meetings. Study participants will not be identified in any publication.

A summary of the trial results will be placed on the trial website.

Anonymised individual patient data and imaging will be made available to data pooling projects, including nitric oxide acute stroke pooling project, BASC, OAST, and VISTA.[56-61] Similarly, summary/group data will be shared with systematic reviews including Cochrane BASC and NO.[16, 62, 63]

USER AND PUBLIC INVOLVEMENT

A stroke patient representative was a member of the team that designed the trial, and is a grant applicant and member of the Trials Steering Committee. They have contributed to development of trial paperwork, including the Patient Information Sheet, and will contribute to the primary publication resulting from the trial.

STUDY FINANCES

Funding source

This study is funded by the British Heart Foundation

Participant stipends and payments

Participants will not receive any payment or expenses for taking part in this study.

Appendix A. Modified Rankin Scale

All investigators should gain sufficient training and certification to measure mRS.

0 No symptoms at all.
1 No significant disability, despite symptoms; able to carry out all usual duties and activities.
2 Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance.
3 Moderate disability; requiring some help, but able to walk without assistance.
4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention.
6 Dead.

Score 1 to 6. Death is assigned 6.

See [64, 65]

Appendix B. Glasgow Coma Scale

Eye movement

1 = None
2 = To pain
3 = To speech
4 = Spontaneous

Verbal response

1 = None
2 = Incomprehensible
3 = Inappropriate
4 = Confused
5 = Orientated

Motor response

1 = None
2 = Extension
3 = Flexor response
4 = Withdrawal
5 = Localises pain
6 = Obeys commands

Total score out of 15 (range 3 – 15). Death is assigned 2.

See [66]

Appendix C. National Institutes of Health Stroke Scale

All investigators should gain sufficient training and certification to measure NIHSS.

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort). (Please also see http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf for pictures associated with this score)

1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.

0 = **Alert;** keenly responsive.

1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond.

2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped).

3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.

1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.

0 = **Answers** both questions correctly.

1 = **Answers** one question correctly.

2 = **Answers** neither question correctly.

1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.

0 = **Performs** both tasks correctly.

1 = **Performs** one task correctly.

2 = **Performs** neither task correctly.

2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.

0 = **Normal.**

1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present.

2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.

0 = **No visual loss.**

1 = **Partial hemianopia.**

2 = **Complete hemianopia.**

3 = **Bilateral hemianopia** (blind including cortical blindness).

4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.

0 = **Normal** symmetrical movements.

1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling).

2 = **Partial paralysis** (total or near-total paralysis of lower face).

3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).

5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.

0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds.

1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.

2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.

3 = **No effort against gravity;** limb falls.

4 = **No movement.**

UN = **Amputation** or joint fusion, explain: _____

5a. Left Arm

5b. Right Arm

6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.

0 = **No drift;** leg holds 30-degree position for full 5 seconds.

1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed.

2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity.

3 = **No effort against gravity;** leg falls to bed immediately.

4 = **No movement.**

UN = **Amputation** or joint fusion, explain: _____

6a. Left Leg

6b. Right Leg

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.

In case of blindness, test by having the patient touch nose from extended arm position.

0 = **Absent.**

1 = **Present in one limb.**

2 = **Present in two limbs.**

UN = **Amputation** or joint fusion, explain: _____

8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.

0 = **Normal;** no sensory loss.

1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched.

2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.

9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.

0 = **No aphasia;** normal.

1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response.

2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response.

3 = **Mute, global aphasia;** no usable speech or auditory comprehension.

10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.

0 = **Normal.**

1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty.

2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.

UN = **Intubated** or other physical barrier,
explain:_____

11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.

0 = **No abnormality.**

1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities.

2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.

Score out of 42 (range 0-42). Death is assigned +43.

See [67]

Appendix D. Barthel Index

Task	Criteria	Score
Bowels	Incontinent	0
	Occasional accident (once per week)	5
	Continent	10
Bladder	Incontinent, or catheterised and unable to manage alone	0
	Occasional accident (maximum once per 24 hours)	5
	Continent	10
Grooming	Needs help with personal care	0
	Independent face/hair/teeth/shaving (implements provided)	5
Toilet use	Dependent	0
	Needs some help, but can do something alone	5
	Independent (on and off, dressing, wiping)	10
Feeding	Unable	0
	Needs help cutting, spreading butter, etc.	5
	Independent	10
Transfer (bed to chair and back)	Unable, no sitting balance	0
	Major help (one or two people, physical), cab sit	5
	Minor help (verbal or physical)	10
	Independent	15
Mobility	Immobile	0
	Wheelchair independent, including corners	5
	Walks with help of one person (verbal or physical)	10
	Independent (but may use any aid: for example stick)	15
Dressing	Dependent	0
	Needs help but can do about half unaided	5
	Independent (including buttons, zips, laces, etc.)	10
Stairs	Unable	0
	Needs help (verbal, physical, carrying aid)	5
	Independent	10
Bathing	Dependent	0
	Independent (or in shower)	5

Score out of 100 (range 0-100). Death is assigned -5.

See [68, 69]

Appendix E. EuroQoL, EQ-5D

Score 1 – 3 for each group/dimension.

Group 1
1. I have no problems in walking about
2. I have some problems in walking about
3. I am confined to bed

Group 2
1. I have no problems with self care
2. I have some problems with washing or dressing
3. I am unable to wash or dress myself

Group 3
1. I have no problems performing my usual activities (e.g. work, study, housework, family or leisure activities
2. I have some problems performing usual activities
3. I am unable to perform my usual activities

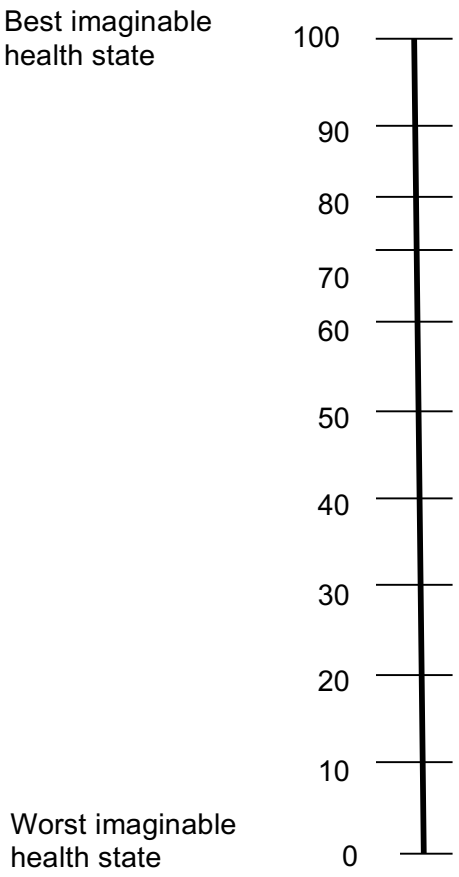
Group 4
1. I have no pain or discomfort
2. I have moderate pain or discomfort
3. I have extreme pain or discomfort

Group 5
1. I am not anxious or depressed
2. I am moderately anxious or depressed
3. I am extremely anxious or depressed

The Health Utility Scale (HUS) is derived from the EQ-5D. Death is assigned 0.

See [70, 71]

Health state today by visual analogue scale (best imaginable to worst imaginable)



Score single integer between 0 and 100. Death is assigned -1.

See [72]

Appendix F – Adult lifestyles and function interview (ALFI) - MMSE

QUESTIONS	Maximum score	Patient's score	[73]
What is the year/month/day/date/time?	5		
Where are we now – country/town/district/building?	4		
I am going to name three objects and I want you to repeat them after me: apple, table and coin. Please repeat them.	3		
Can you subtract 7 from 100 (93, 86, 79, 72, 65)?	5		
Can you recall the three words I asked you to remember?	3		
Can you repeat "No ifs, ands or buts"?	1		
What is the thing called that you are speaking into as you talk to me?	1		
Total score	22		

Appendix G. Cognitive Testing

TICS-M

Please note that this test is designed for telephone use. In the event follow up is done in person the entire test must be completed verbally, i.e. the memory words must not be shown to the patient.

Orientation:

1(a). What day of the week is it?	Day	☐
(b). What is today's date?	Date	☐
	Month	☐
	Year	☐
(c). What season are we in?	Season	☐
2. What is your age?	Age	☐
3. What is your telephone number?	Correct	☐

Registration/ Free Recall:

4. I am gong to read you a list of 10 words. Please listen carefully and try to remember them. When I am done, tell me as many as you can in any order. Ready?

Cabin	☐
Pipe	☐
Elephant	☐
Chest	☐
Silk	☐
Theatre	☐
Watch	☐
Whip	☐
Pillow	☐
Giant	☐

Now tell me the words you can remember

Attention/Calculation:

5. Please take away 7 from 100	93	☐
Now continue to take 7 away from what	86	☐
you have left over until I ask you to stop	79	☐
	72	☐
	65	☐
6. Please count backwards from 20 to 1	No mistakes	☐

Comprehension, Semantic and Recent Memory:

7. What do people usually use to cut paper?	Scissors	☐
8. What is the prickly green plant found in the desert?	Cactus	☐
9. What is the name of the reigning monarch?	Correct Name	☐
10. What is the opposite direction to east?	West	☐
11. What is the surname of the prime minister?	Correct Name	☐

Language/Repetition:

12. Please listen carefully and repeat this: "Methodist episcopal"	Exactly right	☐

Delayed Recall:

13. Please repeat as many of the 10 words I asked you to remember earlier

Cabin	☐
Pipe	☐
Elephant	☐
Chest	☐
Silk	☐
Theatre	☐
Watch	☐
Whip	☐
Pillow	☐
Giant	☐

Score 1 point for each correct answer.

Score _____

Score out of 39 (range 0-39). Death is assigned -1.

See [74]

Concentration (from MMSE) Spell WORLD backwards (or language specific equivalent)

Score out of 5

Verbal Fluency

Now you have 1 minute to name as many animals as you can think of. Ready? Start now!

Write down each word and score 1 mark for each animal named. Do not score repetitions.

Score 0, 1, 2, 3, 4, 5 etc. Death is assigned -1.

See [75]

Appendix H. Zung Depression rating Scale (short)

With scores:	Seldom or never	Some of the time	Good part of time	Most of time
I feel down-hearted and blue	1	2	3	4
I have trouble sleeping at night	1	2	3	4
Morning is when I feel best	4	3	2	1
I can eat as much as I used to	4	3	2	1
I get tired for no reason	1	2	3	4
I find it difficult to make decisions	1	2	3	4
I feel hopeful about the future	4	3	2	1
I feel that I am useful and needed	4	3	2	1
My life is somewhat empty	1	2	3	4
I still enjoy the things I used to do	4	3	2	1

Short Zung IDS Index = 100 x Total / 40. Depression => 70. Death is assigned 102.5.

See [68, 76, 77]

Appendix I. Frailty score on baseline neuroimaging

Component items: previous infarct (cortical or subcortical), atrophy, white matter changes

None	No items present
Mild-moderate	1-2 items present
Severe	All items present

Score out of 2 (range 0-2). Death is assigned 3.

See Wardlaw *et al*. Submitted for publication.

Appendix J. Small vessel disease score on baseline neuroimaging

Component items: white matter hyperintensities (graded), lacunes

None	No items present
Mild-moderate	Mild-moderate WMH and/or lacune(s)
Severe	Severe WMH and lacune(s)

Score out of 2 (range 0-2). Death is assigned 3.

See [78]

Appendix K: Expected events not subject to expedited reporting

After GTN and/or stroke the following events are expected and therefore not subject to expedited reporting

Cardiovascular

Acute coronary syndrome (ACS)
Angina: stable
Angina: unstable (UA)
Angina: type undefined
Atrial fibrillation (AF) or atrial flutter
Bradycardia
Cardiac (mural) thrombus
Cardiac dysrhythmia
Cardiac failure
Carotid dissection
Carotid stenosis: carotid endarterectomy
Carotid stenosis: no carotid endarterectomy
Carotid stenosis: carotid stenting
Chest pain (NOT cardiac)
Collapse
Deep vein thrombosis (DVT)
Endocarditis
Heart failure
Hypertension
Hypotension
Left atrial myxoma
Left ventricular failure (LVF)
Myocardial Infarction: NSTEMI
Myocardial Infarction: STEMI
Myocardial Infarction: type undefined
Patent foramen ovale (PFO)
Pericardial bleed
Peripheral Arterial Disease (PAD) / ischaemic limb
Sudden Cardiac Death (SCD)
Supra-ventricular Tachycardia
Systemic embolism
Tachycardia
Vasovagal episode
Vascular event (not otherwise specified)
Ventricular tachycardia (VT)

Nervous System

Agitation
Alzheimer's disease (AD)
Anxiety / apprehension
Brain Tumour: primary
Brain Tumour: secondary
Cerebral oedema
Cognitive decline
Complication of initial stroke
Cortical vein thrombosis
Deafness / hearing loss
Dementia: type undefined
Depression
Dizziness
Dysarthria
Dysphagia
Dysphasia
Extension of initial ischaemic stroke
Extradural haematoma / bleed (EDH)
Extraspinal bleed
Functional / Mimic / Pseudo Stroke
Haemorrhagic stroke - primary haemorrhage/bleed
Haemorrhagic transformation of infarction (HTI): HT1 or HT2
Haemorrhagic transformation of infarction (HTI): HT1
Haemorrhagic transformation of infarction (HTI): HT2
Haemorrhagic transformation of infarction (HTI): PH1 or PH2
Haemorrhagic transformation of infarction (HTI): PH1
Haemorrhagic transformation of infarction (HTI): PH2
Haemorrhagic transformation of infarction (HTI): type undefined
Hallucinations
Headache
Hydrocephalus
Intracranial aneurysm
Intraspinal bleed / haematoma
Intraspinal infarct
Ischaemic stroke: no blood
Ischaemic stroke with HTI: HT1 or HT2
Ischaemic stroke with HTI: HT1
Ischaemic stroke with HTI: HT2
Ischaemic stroke with HTI: PH1 or PH2
Ischaemic stroke with HTI: PH1
Ischaemic stroke with HTI: PH2

Migraine
Nerve Entrapment
Neurological deterioration
Neurological Event: NOT stroke/TIA
Stroke: type undefined
Sedation
Seizure / Convulsions
Sensory loss
Stroke type: type unknown
Subarachnoid haemorrhage (SAH)
Subdural haematoma / bleed (SDH)
Transient Ischaemic Attack (TIA) - imaging negative
Transient Ischaemic Attack (TIA) - imaging positive
Transient Ischaemic Attack (TIA) - no imaging
Vascular dementia (VaD)
Vertigo
Visual loss
Weakness

Respiratory

Acute respiratory failure: type 1
Acute respiratory failure: type 2
Acute respiratory failure: type undefined
Asthma
Bronchitis
Bronchospasm
Chest infection
Chronic obstructive pulmonary disorder (COPD)
Chronic obstructive pulmonary disorder (COPD): exacerbation
Epistaxis
Emphysema
Haemoptysis
Hypoxia
Interstitial pneumonitis
Pleural effusion
Pneumonia
Pneumothorax
Carcinoma: primary lung
Pulmonary embolism (PE)
Pulmonary fibrosis
Pulmonary haemorrhage
Respiratory tract infection, lower (LRTI)

Respiratory tract infection, upper (URTI)
Secondary lung cancer
Shortness of breath

Gastro-Intestinal

Abdominal pain
Bowel ischaemia
Carcinoma: bowel
Cholecystitis
Colitis
Constipation
Diarrhoea
Diverticulitis
Dysphagia
Gall stones
Gastroenteritis
Gastrointestinal disturbance
Gastrointestinal infarction
Haemorrhoids: bleeding
Haematemesis
Heartburn
Hepatitis
Hernia
Incontinence: faecal
Liver/hepatic impairment/dysfunction
Lower GI bleed
Melaena
Nausea
Oesophagitis
Oral ulceration
Pancreatitis
Peptic Ulcer
Carcinoma: primary liver
Rectal bleed
Liver metastasis
Stomatitis
Upper GI bleed
Vomiting
Weight loss

Genito-Urinary

Carcinoma: bladder
Glomerulonephritis
Haematuria
Incontinence: urinary
Kidney stones
Penile bleed
Carcinoma: renal primary
Prostate cancer
Renal cyst
Kidney/renal impairment/failure/disease: acute (ARF)
Kidney/renal impairment/failure/disease: chronic (CKD)
Kidney/renal impairment/failure/disease: undefined
Sexual dysfunction
Urinary retention
Urinary tract infection (UTI)
Vaginal bleed

Haematological

Acquired haemophilia
Agranulocytosis/granulocytopenia
Anaemia: type undefined
Anaemia: aplastic
Anaemia: microcytic
Anaemia: macrocytic
Haemoglobin drop: asymptomatic
Haemoglobin drop: dilutional
Haemoglobin drop: unidentified
Eosinophilia
Hypersensitivity inc. oropharangeal swelling, urticaria, angiodema etc.
Leukopenia
Lymphadenopathy
Methaemoglobinaemia
Neutropaenia
Pancytopenia
Polycythaemia
Thrombocytopenia
Thrombotic thrombocytopenic purpura (TTP)
Vasculitis

Immunological

Haematological
Allergic reaction
Anaphylactic reaction
Hypersensitivity

Metabolic / Endocrine

Acid base disturbance
Dehydration
Diabetes mellitus (Type II)
Electrolyte disturbance
Hyperglycaemia
Hyperthyroidism
Hyperuricaemia
Hypoglycaemia
Hypothyroidism

Musculoskeletal / Cutaneous

Arthritis / arthralgia
Bleed: gingival
Bleed: skin
Bruising, ecchymoses
Bullous dermatitis
Cellulitis
Cramps
Eczema
Flushing
Fractured bone
Gout
Hypersensitivity
Intra-articular bleed, haemarthrosis
Intramuscular bleed with compartment syndrome
Intramuscular bleed without compartment syndrome
Muscle twitching
Myalgia
Myositis
Osteoarthritis
Pressure ulcer
Pruritis
Rash

Ocular

Extra-ocular bleed: conjunctival, subconjuctival

Intra-ocular bleed: retinal, vitreous

Retroperitoneal

Retroperitoneal bleed

Miscellaneous

Bacteraemia - septicaemia

Death unattended

Dehydration

Diaphoresis

Drug error

Extracranial bleeding (not GI haemorrhage)

Fall - collapse

Fatigue - malaise

Fever

Haemorrhage of operative wound

Infection (not otherwise specified)

Lymphadenopathy

Bleed: other (please specify bleed location)

Other. (please state medical condition)

Self harm

Septicaemia

Suicide

Trauma

Tumour: benign

Tumour: malignant

Appendix L. Qualitative Additional Research Study

Ethics of Stroke Trials within Ambulance Services

We will investigate important aspects of the ethics and conduct of ambulance trials in the prehospital setting by exploring the experiences and perceptions of patients and paramedics participating in the RIGHT-2 trial within the East Midlands region. Our feasibility study showed that paramedics were concerned about time constraints, diagnostic uncertainty and information needs of patients and relatives during the process of informed consent [23].

In this qualitative sub-study, we would like to explore such issues, in order to improve the design of future ambulance based trials in the country.

Aim

To investigate the experiences, perceptions and challenges reported by patients and paramedics in the ethics of recruiting patients to an ambulance based hyper acute stroke trial (RIGHT-2).

Design

Qualitative interview study with patients and paramedics.

Participants

Approximately 15 patients within the East Midlands region and 15 paramedics from the East Midlands Ambulance Service NHS Trust participating in the main RIGHT-2 study will be invited to take part. They will be informed about the additional research study by researchers during the investigator meetings and by telephone, post or email. Contact details will be recorded for those who express an interest.

Inclusion/Exclusion Criteria for Patients

Patients will be eligible who have survived a stroke and have participated in the randomised controlled trial involving ambulance services in the East Midlands region (RIGHT-2 trial), with the mental capacity to be approached and the ability to participate in an interview, and who consent to take part in this study.

Patients will be recruited from any of the six counties (Lincolnshire, Nottinghamshire, Derbyshire, Leicestershire, Rutland and Northamptonshire) served by East Midlands Ambulance Service NHS Trust (EMAS). We wish to gain a wide spectrum of views from patients to ensure representation from each of the six counties or specific patient groups therefore no other inclusion or exclusion criteria apply.

Inclusion/Exclusion Criteria for Paramedics

Paramedics employed by East Midlands Ambulance Service NHS Trust will be eligible to participate if they have completed the RIGHT-2 training and have preferably attempted to randomise at least one patient into the RIGHT-2 trial.

Study Regimen

Patients
This additional research study will start once the main study is underway. Patients will have participated in the main study and been discharged from hospital, well enough to participate in an interview.

Patients will be approached for an expression of interest by one of two methods:

- Patients may be approached during their initial hospital admission by a member of the research team asking for an expression of interest. This information will be passed on to the University research team using the expression of interest document.
- The additional research study will be explained at the end of the Day-90 telephone follow up for an initial expression of interest. This information will be passed on to the University research team using the expression of interest document.

This will be followed up by the central research team who will then contact the participant within 10 working days, send out the study pack consisting of a covering letter, information sheet and a consent form with a returnable pre-paid envelope to the patient giving them time to consider whether to participate in an interview.

Paramedics
Paramedics, who have shown an interest and preferably have attempted to randomise at least one patient, will be contacted via telephone or email with details of the additional research study and contact details of the researchers should they be interested in taking part.

All Participants
Following initial expression of interest to participate and receipt of the information pack, researchers will explain details of the additional research study and what participation will entail. Those who give informed consent will be eligible to be interviewed.

From a practical perspective, and from our previous experience of conducting interview based studies in this research setting, a sample size of around 10-15 patients and 10-15 paramedics will allow us to explore the important issues and themes related to the study question, and to gather sufficient data to achieve theoretical saturation, although we will continue to recruit participants until no further new themes emerge.

Data collection
Interviews will be carried out at a time and place convenient to the participant (for example: patient's home address, university premises, ambulance station as appropriate). After rechecking consent, including permission to audio record the interview using a digital voice recorder, data will be collected using semi-structured interview schedules (see corresponding working practice document: ESTA Paramedic Interview Schedule, ESTA Patient Interview Schedule). The questions will act as a guide only and the interviewer will seek to explore other relevant issues that participants raise.

Interviews will last approximately 60 minutes and where permission is not given to record digitally, handwritten notes will be taken.

Data processing and analysis

Digital voice recordings and/or notes of each interview will be transferred to a password-protected folder on the investigator's University computer. Transcripts will be anonymised, with pseudonyms used for personal and place names. Systematic, thematic analysis will be performed. Interview data will be treated as reporting actual experiences and perceptions of the interview participants.

Original audio recordings will be stored securely in an archive accessible to the investigators, and will be destroyed 7 years after the last publication arising from the sub-study. These procedures are in accordance with the University's research policy.

Appendix M. Qualitative Additional Research Study 2 - Exploring Clinical Trials in Ambulance Services

Pre-hospital clinical trials are essential to develop effective emergency healthcare to complement the development of in-hospital interventions for time-critical conditions. With increasing pressures placed on ambulance services, understanding the place research has in the pre-hospital setting and how it is conducted from the context of the staff who work in this high-pressured environment is crucial due a to a lack of evidence in this field.

This qualitative research study will explore the perceptions and experiences of Paramedics taking part in a large multi-centre ambulance-based stroke trial (RIGHT-2), with a key interest to understand the strengths and challenges, and differences between ambulance services in order to support the development of future large scale collaborative trials.

Aim

It is the aim of this qualitative study to:

- Explore the perceptions and experiences of Paramedics taking part in a national research trial to test the safety and efficacy of early provision of pre-hospital stroke care.
- Develop an understanding of how research activity is perceived by Paramedics across multiple United Kingdom (UK) ambulance service trusts to inform the future design of ambulance based research trials.

Design & Participants

Information will be sought through interviewing Paramedics across the UK NHS Ambulance Services who are participating in the RIGHT-2 trial.

A sample of approximately 16 Paramedics from ambulance services taking part in the RIGHT-2 trial will be sought purposively and interviewed with the aim of understanding the rationale to their participation, experiences and perceptions of taking part in pre-hospital research.

This study will commence once the main trial is underway to ensure Paramedics from each ambulance service are afforded time to attend, screen potentially eligible patients and attempt randomisation in to RIGHT-2.

Inclusion / Exclusion Criteria

Paramedics will be eligible to participate if have they expressed interest in the RIGHT-2 trial and have preferably attempted to randomise at least one patient in to RIGHT-2.

Paramedics will be invited to participate by email that will include the details of the study. Following the return of an expression of interest to investigators, Paramedics will receive an information leaflet containing more information on the study and what their participation will entail.

Unless contact is received from the interested Paramedic following receipt of the study leaflet, investigators will email Paramedics 10 working days after sending the information leaflet to confirm their intention to participate. Where informed consent is gained, interviews will be arranged at a convenient time and place.

Data Collection

Interviews will be carried out at a time and place convenient to the Paramedic (for example: ambulance station, home address or by telephone). Consent will be confirmed, which will include permission to record the interview using a digital-voice recorder and the writing of field notes.

Data will be collected using semi-structured interviews (see corresponding working practice document detailing the interview schedule). The questions will serve as a guide only and the interviewer will seek to explore other relevant issues raised.

Interviews will last approximately 60 minutes. Handwritten notes will be taken where permission to record with a digital-voice recorder is declined.

Data Analysis

Digital voice recordings and/or notes of each interview will be transferred to a password-protected folder on the investigator's University computer. Original audio recordings will be erased once the interview has been transcribed, checked for accuracy and analysis is complete.
Transcripts will be anonymised, with pseudonyms used for personal and place names. Systematic, thematic analysis will be performed. Interview data will be treated as reporting actual experiences and perceptions of the interview participants.

Other research data will be stored securely in an archive accessible to the investigators, and will be destroyed 7 years after the last publication arising from the study. These procedures are in accordance with the University's research policy.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

Trial Statistician: (name)_____

Signature:_____

Date: _____

Trial Pharmacist: (name)_____

Signature:_____

Date: _____

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