

## Clinical Study

# Determining the Feasibility of Ambulance-Based Randomised Controlled Trials in Patients with Ultra-Acute Stroke: Study Protocol for the “Rapid Intervention with GTN in Hypertensive Stroke Trial” (RIGHT, ISRCTN66434824)

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Received 8 July 2012; Revised 14 September 2012; Accepted 21 September 2012

Academic Editor: Chelsea S. Kidwell

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**Background.** Time from acute stroke to enrolment in clinical trials needs to be reduced to improve the chances of finding effective treatments. No completed randomised controlled trials of ambulance-based treatment for acute stroke have been reported in the UK, and the practicalities of recruiting, consenting, and treating patients are unknown. **Methods.** RIGHT is an ambulance based, single-blind, randomised controlled trial with blinded-outcome assessment. The trial will assess feasibility of using ambulance services to deliver ultra-acute stroke treatments; a secondary aim is to assess the effect of glyceryl trinitrate (GTN) on haemodynamic variables and functional outcomes. Initial consent, randomisation, and treatment are performed by paramedics prior to hospitalisation. Patients with ultra-acute stroke ( $\leq 4$  hours of onset) are randomised to transdermal GTN (5 mg/24 hours) or gauze dressing daily for 7 days. The primary outcome is systolic blood pressure at 2 hours. Secondary outcomes include feasibility, haemodynamics, dependency, and other functional outcomes. A nested qualitative study is included. **Trial Status.** The trial has all relevant ethics and regulatory approvals and recruitment started on February 15, 2010. The trial stopped recruitment in December 2011 after 41 patients were recruited. **Trial Registration.** The trial registration number is ISRCTN66434824 and EudraCT number is 2007-004766-40.

## 1. Background

Finding acute interventions which reduce early brain damage and improve outcome after acute stroke is of major importance and has proved challenging. Irreversible brain damage starts in the first minutes to hours after a stroke [1] and acute stroke treatments can be highly time dependent; outcomes after stroke thrombolysis are better when treatment is given early [2]. Ambulance administration of emergency treatment is standard in acute medical emergencies such

as acute myocardial infarction and asthma; thrombolysis for MI was given 45 minutes earlier if administered in an ambulance than at hospital [3]. Treatments for acute ischaemic stroke (AIS) are not routinely administered prior to hospital since current therapies reduce haemostasis (e.g., aspirin and alteplase) and need neuroimaging to exclude primary intracerebral haemorrhage (PICH). However, other potential treatments for acute stroke such as neuroprotection and management of physiological disturbances (e.g., high blood pressure [BP], hyperglycaemia and pyrexia) do not

necessarily need prior neuroimaging and could be delivered before hospitalisation. As benefits of such interventions may be time dependent, prehospital administration could considerably increase treatment efficacy by reducing onset to treatment times.

One completed study (field administration of stroke therapy-magnesium phase 3 clinical trial (FASTMag) pilot) has assessed the feasibility of ambulance administration of intravenous magnesium (a potential neuroprotectant) [4]; this US open-label uncontrolled study found that it was possible to enroll, consent, collect basic clinical details, and administer treatment in 20 patients with acute stroke (<12 hours of ictus) [5]. The main FASTMag trial (<http://www.fastmag.info/>) is now running in Los Angeles. In a different model of healthcare delivery in ultra-acute stroke, scanning, diagnosis, and treatment may be delivered at the emergency site using an ambulance specifically equipped with computed tomography scanner, point-of-care laboratory, and medical and nursing staff [6, 7] However, no data are available on the practicality, logistics (patient recruitment and paramedic involvement), diagnostic accuracy, and consent issues of performing trials in the UK ambulance environment in patients with ultra-acute stroke. More studies are needed in prehospital stroke care as highlighted at a European Commission Workshop in 2005 [8].

High blood pressure (BP > 140/90 mmHg) is common in AIS and PICH, and independently associated with a poor outcome [9–11]. These observational data imply that lowering an elevated BP could improve outcome, providing cerebral blood flow (CBF) is not reduced in the presence of dysfunctional autoregulation. However, a Cochrane meta-analysis and a recently completed study of angiotensin receptor antagonist (candesartan) in acute stroke showed no evidence of benefit with drugs used to deliberately alter blood pressure [12, 13]. While the results of large ongoing trials such as ENOS [14] and INTERACT-2 (<http://clinicaltrials.gov/show/NCT00716079>) are awaited, these studies are hospital-based and cannot therefore recruit patients in the ultra-acute period immediately after stroke onset, and so cannot assess the safety and efficacy of immediate treatment. Administration of treatment prior to hospital, for example, in the ambulance, would reduce delay providing that treatment could be given to patients with either AIS or PICH (i.e., treatment did not alter thrombosis/haemostasis) and those with dysphagia (i.e., treatment did not require a formal swallowing assessment and oral administration).

We have developed the use of transdermal GTN (5 mg per day, a nitric oxide donor) for lowering BP in acute stroke in three pilot/phase II randomised controlled trials [15–17]. Nitric oxide is a candidate treatment for stroke being a key endogenous regulator of CBF and tissue perfusion (in part through modulating pial vessel tone thereby potentially improving collateral blood flow) and has neuroprotective properties in experimental stroke [18]. Further, plasma NO levels (nitrate/nitrite) are low in acute stroke and associated with a poor outcome [19, 20] so supplementing NO in stroke might restore its normal functions. The safety and efficacy of GTN is now being

tested in the ongoing MRC-funded “Efficacy of Nitric Oxide in Stroke” (ENOS) trial (<http://www.enos.ac.uk/>), which is also comparing the effect of continuing versus temporarily stopping prior antihypertensive therapy. [14] ENOS has recruited 3273 patients (as of September 14 2012).

We are assessing the feasibility of performing an ambulance-based trial in patients with ultra-acute stroke, a key question for the future testing of potential interventions aimed at neuroprotection and physiological control, by performing a randomised controlled trial comparing GTN versus no GTN. The data relating to GTN will provide further safety data for developing transdermal GTN as a treatment modality in ultra-acute stroke.

## 2. Methods

### 2.1. Study Aims

**2.1.1. Primary Aim.** The primary aim is to assess the feasibility of using ambulance service practitioners to assess and deliver treatments for stroke in the ultra-acute setting after stroke.

**2.1.2. Secondary Aim.** Assess the effect of GTN use in ultra-acute stroke on safety, clinical, functional, and haemodynamic outcomes.

### Primary Objectives

- (i) To report the proportion of randomised patients with a final diagnosis of ischaemic stroke, primary intracerebral haemorrhage, or transient ischaemic attack.
- (ii) To assess the additional time taken by research paramedics for study related procedures prior to hospital admission.
- (iii) To report the experiences, perceptions, and challenges of a purposive sample of participating paramedics in terms of approaching, consenting, recruiting, and randomising patients to the trial.
- (iv) To assess the proportion of patients randomised and treated according to protocol.
- (v) To assess the characteristics of patients screened by the paramedics for inclusion to the RIGHT study.
  - (a) Proportion of patients screened by the paramedics who were included in the study.
  - (b) Report the common reasons for failing the study eligibility criteria.
- (vi) To assess the characteristics of suspected acute stroke patients admitted to the research sites.
  - (a) Proportion of suspected stroke patients who satisfied the study eligibility criteria.
  - (b) Report the common reasons for failing the study eligibility criteria.

### Secondary Objectives

- (i) To assess the safety and tolerability of GTN in suspected ultra-acute stroke.
- (ii) To compare the difference in peripheral blood pressure, central blood pressure, heart rate, and its derivatives between patients randomised to GTN or no GTN.
- (iii) To compare the difference between GTN and no GTN in death, disability, dependency, mood, cognition, and quality of life.

2.2. *Study Design.* RIGHT is an ambulance-based, prospective, open label, single-blind, single city, randomised controlled trial with blinded outcome assessment (Figure 1).

2.3. *Study Setting.* The study is conducted by the University of Nottingham in collaboration with the East Midlands Ambulance Service NHS Trust (EMAS) and Nottingham University Hospitals (NUH) NHS Trust. Only patients who are transported to the NUH Trust Hospitals (Nottingham City Hospital, Queens Medical Centre Nottingham), which provides service to approximately to 2.5 million residents of Nottingham and its surrounding communities, are eligible for recruitment. Research trained EMAS paramedics from across 12 ambulance stations in Nottingham are taking part in the study.

2.4. *Study Population.* Adult patients with suspected stroke presenting to research trained paramedics and fulfilling the following study criteria are eligible for recruitment.

#### 2.4.1. Inclusion Criteria

- (i) Adult male patients >40 years (to reduce the chance of false positive strokes), female patients >55 years (to exclude potentially pregnant patients).
- (ii) Paramedic assessment of stroke on the basis of positive “Face Arm Speech Test” (FAST) score of 2 or 3 [21, 22].
- (iii) Event  $\leq$ 4 hours of onset (wake up stroke-onset as bed time).
- (iv) Systolic BP  $\geq$ 140 mmHg (any one of the two pre-randomisation readings).
- (v) Consent from patient, next of kin, or paramedic.
- (vi) Patient being transported to RIGHT trial site.

#### 2.4.2. Exclusion Criteria

- (i) Definite need for GTN (e.g., concurrent angina).
- (ii) Definite contraindication for GTN (e.g., dehydration, hypovolaemia).
- (iii) Nonambulatory prior to event onset.
- (iv) Coma (Glasgow Coma Scale, GCS  $\leq$ 8).

- (v) Hypoglycaemia (blood glucose <2.5 mmol/l).
- (vi) Patients who are pregnant or breast feeding.
- (vii) Systolic BP <140 mmHg.

The limited exclusion criteria will result in a streamlined trial with generalisable results (thereby providing external validity).

2.5. *Paramedic Training.* Interested paramedics working for the EMAS NHS Trust attended a training session on the background, eligibility assessment, consent process and study related procedures. A trial folder containing the trial protocol, forms, and documents is maintained at all the 12 participating ambulance stations. Trial recruitment started with 28 trained paramedics from 10 ambulance stations in February 2010; a further 50 paramedics were trained during the trial period to improve recruitment rate. Repeat training sessions are conducted for paramedics who feel a need to refresh their knowledge about the trial. All paramedics were given information about the trial website—<http://www.right-trial.org/>. Regular newsletters about the trial status and important trial related information is sent to all trained paramedics.

2.6. *Screening, Recruitment, and Consent.* The trial was active during regular working hours from Monday to Friday. During out of hours, trial paramedics contact the hospital research staff if there is a potential patient, and recruitment is allowed if hospital research staff are on site, available, and able to perform trial related procedures. Weekend recruitment from 0700 to 1500 hours was also allowed from March 2011 depending on hospital research staff availability.

2.6.1. *In the Ambulance.* In the context of a “999” call for suspected stroke, FAST score of >1, and assessment of study eligibility, verbal consent is taken in the prehospital setting by trained paramedics. Potential patients are approached by the paramedic to take part in the study who explains the trial to the patient by reading out a single page information sheet. The sheet contains information on the purpose of the study, reasons why they have been approached, and what will happen to them if they take part. The research paramedic then asks simple questions about the trial to assess if the patient has understood the trial, that is, if they have the capacity to give consent. These questions cover “what is your diagnosis” (answer: stroke), “what is wrong with your blood pressure” (answer: it is high), and “what is the treatment” (answer: a patch) (G Ford, personal communication). If the patient has understood the trial details and agrees to take part in the study, they are then asked to sign a consent form.

For patients lacking capacity, their relatives, if present, are approached to provide proxy-consent. If the patient is unable to provide consent and there is no relative present, research paramedics give proxy-consent on behalf of patients for the first part of the trial provided a second paramedic or ambulance technician acts as a witness to the consent process and countersigns the form. The initial consent, from patient, relative, or paramedic, covers the period in the ambulance

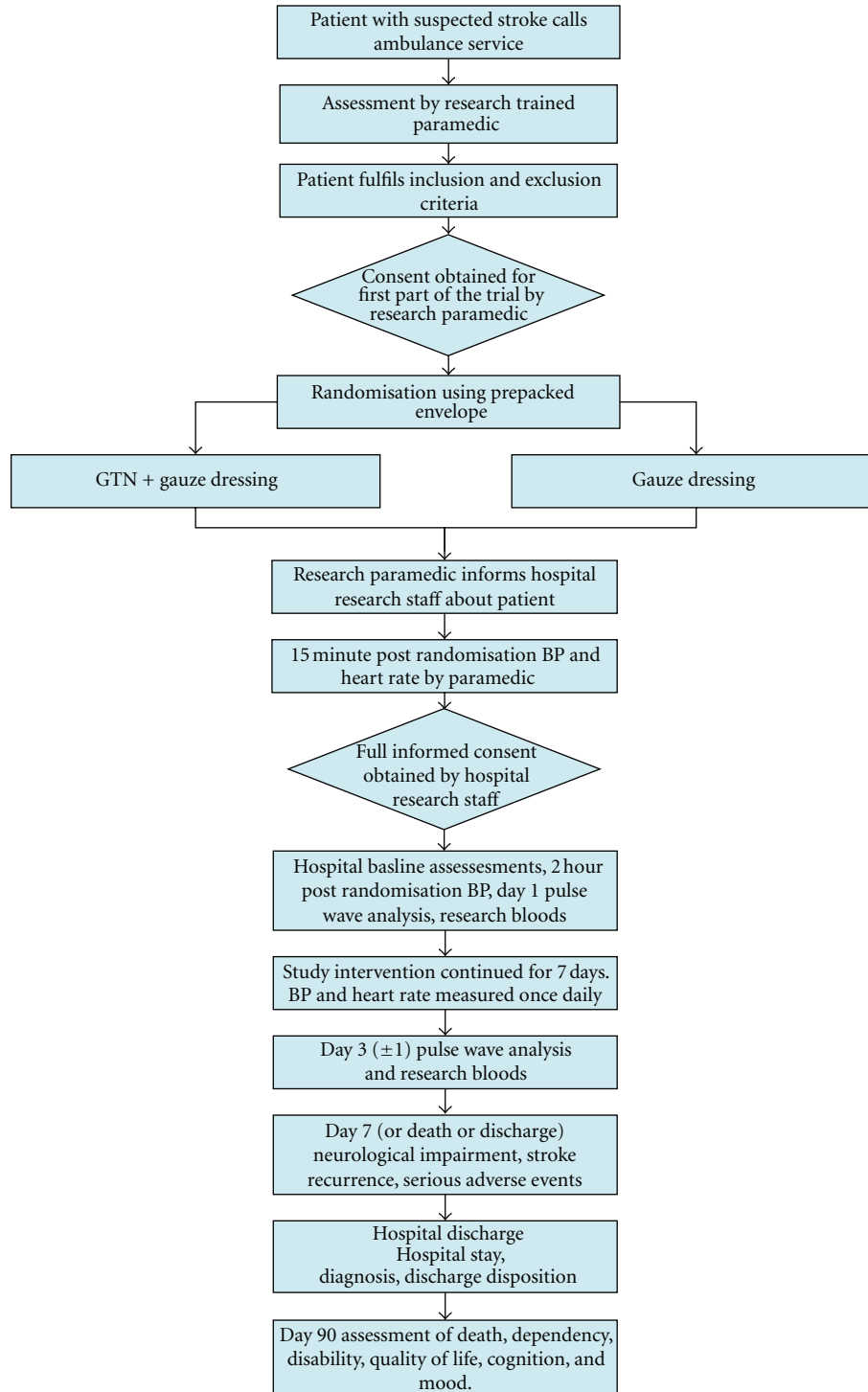


FIGURE 1: Trial flow chart.

(including administration of the first dose of treatment and blood pressure measurement) up to and including admission to hospital.

**2.6.2. At Hospital.** Once the patient arrives in hospital, the hospital researcher discusses the trial, provides a full patient

information sheet, and answers any questions. If the patient is unable to write (e.g., in the presence of dominant hand weakness, ataxia, or dyspraxia), witnessed verbal consent may be recorded on the consent form. If the patient lacks capacity (e.g., in cases of dysphasia, confusion, or reduced conscious level), proxy-consent is sought from a relative. Full informed written consent is obtained from each patient

within 24 hours of the initial consent, that is, before the next treatment dose. If consent is not obtained within 24 hours, trial intervention is withheld after 24 hours but blood pressure readings are taken until consent is obtained.

**2.7. Randomisation.** Each paramedic carries one or two numbered opaque sealed envelopes in a transparent plastic blue folder. The envelope contains trial paperwork (described later) and a second opaque envelope that contains a gauze dressing, with or without a single GTN patch (5 mg); this inner/second envelope is only opened if informed consent is obtained. The research paramedic will not know or be able to guess the treatment allocation prior to opening the opaque envelope. This process amounts to simple randomization with no stratification or minimisation.

### 2.8. Study Intervention

**2.8.1. Investigational Medicinal Product (IMP).** The study intervention is transdermal glyceryl trinitrate (GTN) patch (5 mg) or none (control). GTN is given in the form of Nitro-Dur 0.2 mg/hr (Schering-Plough Ltd) with the patch placed on the back or shoulder. Standard NHS supplies are used. Since no companies manufacturing GTN patches were willing to provide a placebo patch, the trial is open-label. The GTN patch is covered with a gauze dressing. Similarly, patients randomised to the control group have a gauze dressing placed in a similar position to provide blinding of treatment to the patient.

GTN patches are dispensed by Nottingham City Hospital pharmacy. For prehospital use, the IMP is dispensed in a numbered trial envelope sealed in a plastic transparent folder containing gauze dressing with or without GTN patch along with trial documents (ambulance information sheet, consent forms, ambulance baseline case report form (CRF), inclusion and exclusion criteria sheet, and a noninclusion form (to be completed for patients who were screened but not included in the trial)). The trial envelopes are stored in the drug cupboard of participating ambulance stations. Each research paramedic carries one or two envelopes when on duty after signing a log sheet. The envelopes are picked up from the ambulance station at the beginning of the shift (as with opiates and cardiac thrombolytics) and returned at the end of the shift.

In hospital, six gauze dressings with or without GTN patches for each randomisation number are dispensed by the pharmacy and kept in the acute stroke unit clinical trial drug safe for hospital use. These are logged with batch number and expiry date, and when they are given to patients.

**2.8.2. Trial Treatment and Regimen.** Trial treatment with gauze dressing, with or without transdermal GTN patch (5 mg), is administered daily for 6 days (amounting to seven treatments). Treatment is given on top of “best guideline hospital care,” including alteplase (as appropriate after AIS) and multimodal secondary prevention. Study medication may be stopped if the patient withdraws consent, for safety reasons, or if unacceptable adverse events develop. All prior

treatments may be continued at the discretion of the treating physician.

**2.9. Study Measures and Followup (Table 1).** Peripheral blood pressure measurements are performed using semiautomated machines; the equipment varies in the ambulance whilst an Omron 705 CP or 705 CP II is used in hospital [17]. All measures are taken in duplicate in immediate succession. Central blood pressure and aortic compliance are performed in hospital using the pulse wave analysis (PWA) system (Sphygmocor, Sydney, Australia) [16, 17]. Blood samples are taken at baseline (EDTA and clotted) and on day 3 ± 1 (EDTA and clotted/serum). Serum and EDTA samples are centrifuged prior to freezing and stored locally in a freezer at -80 degree Celsius.

**2.10. Protocol Violations.** A protocol violation is a deviation from the trial protocol where a patient is included outside the inclusion/exclusion criteria for the trial, and where deviations from the protocol could affect the trial significantly. A list of violations is listed below.

- (1) Male patient ≤40 years (to reduce the chance of recruiting non-stroke patients and female patient ≤55 years (to avoid potential pregnant and child bearing patients).
- (2) Randomisation >4 hours from onset of symptoms.
- (3) FAST score <2 at randomisation.
- (4) Systolic BP <140 mmHg at randomisation (neither of the two readings).
- (5) GCS ≤8 at randomization.
- (6) Failure to obtain consent or proxy consent for patient participation as specified in the protocol.
- (7) Patient transferred to a nontrial site after randomisation.
- (8) Patient was nonambulatory prior to symptom onset.
- (9) Patient pregnant or breastfeeding.
- (10) Definite need for GTN.
- (11) Contraindication to GTN use.
- (12) Blood glucose <2.5 at randomisation.
- (13) Patient involved at time of randomisation or within 3 months in another medicinal clinical trial.
- (14) Patient does not receive the first randomised treatment.
- (15) Hospital consent for continued participation in hospital is not obtained within 24 hours of admission.

**2.11. Nested Qualitative Study.** We are systematically examining the experiences, perceptions, and challenges reported by a purposive sample of 14 participating paramedics in terms of approaching, consenting, recruiting, and randomising patients to the trial; collaborative working with researchers in an ultra-acute stroke trials; and implications

TABLE 1: Study measures.

Event and timing (day)	1	3 ± 1	7 ± 1	Hospital discharge	90 ± 7
Randomisation	+				
Informed consent	+				
BP and heart rate*	+	+	+		
Scandinavian stroke scale (impairment)	+		+		
Pulse wave analysis	+	+			
Serious adverse events			+	+	+
Diagnosis				+	
Disposition				+	+
Serum S-100 protein	+	+			
Modified rankin scale	+				+
Barthel index					+
Mini mental status examination					+
EuroQOL					+
Zung depression scale					+

\*BP and heart rate assessed daily till day 7.

for future studies. Semistructured interviews are being conducted by S. Ankolekar, transcribed verbatim, and analysed using thematic content analysis.

**2.12. Pharmacovigilance.** All adverse events are assessed for their seriousness and causality to treatment by SA. A serious adverse event (SAE) form is completed for each individual SAE, as defined using standard definitions and reported to the coordinating centre. All SAEs are reviewed by the Chief Investigator (PB). Where an SAE is felt to fall under the definition of a Suspected Unexpected Serious Adverse Reactions (SUSAR), expedited reporting is made to the UK Medicines and Health Regulatory Authority (MHRA) and Research Ethics Committee.

**2.13. Nontrial Patients.** Case notes and ambulance report forms of 41 consecutive patients admitted via the ambulance services between September 2011 and January 2012, directly to the Nottingham City Hospital Stroke Unit but not recruited into the RIGHT study, and whose clinical characteristics match the RIGHT study eligibility criteria, are being reviewed to compare treatment and transfer timings between those in the trial and those transferred into hospital by a wider group of paramedics.

## 2.14. Outcome Measures

**2.14.1. Primary.** Comparison of systolic blood pressure at 2 hours post randomisation between GTN and no GTN groups.

This outcome was chosen since it represents the sum of the trial feasibility and intervention, that is, the ability to identify, recruit, randomise, treat with GTN or control, and make measurements in patients with ultra-acute presumed stroke in an ambulance setting, and hand them over to hospital staff. The 2 hour time reflects the time to peak effect for GTN.

**2.14.2. Secondary.** Comparison between treatment groups.

### Haemodynamic Effects

- (i) BP, heart rate, and their derivatives (pulse pressure, mean arterial pressure, peak pressure, trough pressure, pressure variability, and rate pressure product) on days 1–7.
- (ii) Central BP and aortic compliance on days 1 and 3.

### Functional and Clinical Outcome Measures during Treatment (up to Day 7)

- (i) Stroke impairment (Scandinavian Stroke Scale, SSS [23], chosen as the results will be used to supplement data from the ongoing ENOS trial that also uses the SSS as the stroke severity scale.)
- (ii) Neurological deterioration (Reduction in SSS score >5 points between day 1 and day 7).
- (iii) Recurrence.
- (iv) Symptomatic intracranial events (haemorrhage and mass effect).
- (v) Major extracranial haemorrhage.

### Hospital Events

- (i) Discharge disposition.
- (ii) Length of stay in hospital.

### Day 90 (Final Followup)

- (i) Dependency-modified Rankin scale (mRS) [24].
- (ii) Disability (Barthel Index) [25].
- (iii) Cognition (mini mental state examination) [26].

- (iv) Mood (Zung depression index, ZDI) [27].
- (v) Quality of life (EuroQOL) [28].

#### *Safety Outcomes*

- (i) Death, dependency, and neurological deterioration at day 7.
- (ii) Death at day 90.
- (iii) Headache, hypotension, and hypertension at day 7.
- (iv) Serious adverse events.

#### *Ambulance Trial Logistics*

- (i) Recruitment rate per month.

Proportions of patients.

- (i) Randomised: screened patients.
- (ii) Treated according to protocol: all randomized.
- (iii) Reasons for not enrolling (presence of exclusion criteria and refusal of consent).
- (iv) Final diagnosis of AIS, PICH, or transient ischaemic attack: all randomized.

#### *Timings. Trial patients*

- (i) Time from ictus to randomization.
- (ii) Time from randomisation to hospital arrival.
- (iii) Time from ictus to hospital arrival.

Comparison between trial and nontrial patients.

- (i) Time from ictus to arrival by paramedics at scene of ictus.
- (ii) Time from paramedic arrival at scene of ictus to hospital arrival.
- (iii) Time from ictus to hospital arrival.

#### *Blood samples*

- (i) Surrogate markers of efficacy (e.g., serum S-100 protein [29]).

### **3. Statistical Design and Analysis**

**3.1. Randomisation.** Treatment allocation to the trial envelopes was performed using a variable block size simple randomisation with equal distribution between active and control groups for the planned total of 80 patients.

**3.2. Blinding.** The study is single blind. There is no placebo treatment in this trial. Trial treatment will be applied at a site that is not easily visible to the patient (e.g., upper back). The dressing will be changed each day to blind patients as to their treatment allocation.

Bias will be reduced using multiple strategies: concealment of allocation; patient blinding to GTN (gauze dressing over patch); measurements and followup blinded to treatment assignment; exclusion of patients enrolled in other trials; analysis by intention-to-treat with adjustment for nonrandomised treatment (alteplase).

**3.3. Sample Size Calculation.** Using data from our previous clinical trials with GTN in acute stroke, and assuming alpha (significance) = 5%, power (1-beta) = 90%, difference in SBP at 2 hours 14 (SD 14) mmHg, and randomisation 1:1 for GTN: control, a sample size of 80 will be needed. This sample size should be sufficient to provide convincing evidence on the utility and issues related to performing ambulance-based trials, including diagnosis of stroke and additional timing for research, of assessing the effect of GTN on BP. It should be feasible to enrol 80 patients over 18 months (>1 patient/week).

**3.4. Statistical Analysis.** Data will be tabulated and described as number (frequency %), median (interquartile range), or mean (standard deviation). Data for each treatment group (GTN versus no GTN) will be compared by intention-to-treat. Unadjusted comparisons will be performed using chi-square test (or Fisher's exact test for data with small counts), Mann-Whitney *U* test (ordered categorical data, e.g., mRS [30] with correction for continuity and ties) and students *t* test (continuous data, e.g., SBP). Comparison of systolic blood pressure at 2 hours (primary outcome) between the treatment groups will also be adjusted for baseline SBP, age, and severity (SSS) (using ANCOVA); comparison of the mRS at day 90 will be adjusted for age, severity, stroke type, and alteplase (using multiple regression) [31, 32].

## **4. Trial Regulation and Conduct**

**4.1. Ethics and Clinical Governance.** The trial is being conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (1996), the principles of Good Clinical Practice (GCP), and the UK Department of Health Research Governance Framework for Health and Social care (2005). The trial has approvals from the MHRA (reference 03057/0033/001-0001, dated February 16, 2009), Nottingham Research Ethics Committee-2 (reference 09/H0408/5, dated April 08, 2009), Research & Development Departments at East Midlands Ambulance Service (dated September 18, 2009) and NUH (reference 08SR003, dated September 30, 2009). The trial is sponsored by the University of Nottingham (reference RIS 08022/30592, dated January 12, 2009).

**4.2. Service and User Involvement.** The Nottingham Stroke Patients forum discussed and supported the trial (dated January 11, 2006) and members felt that they would have been willing to take part if affected with a further stroke. The trial has been presented to, and is supported by, the EMAS board.

**4.3. Records and Data Protection.** The investigator (S. Ankolekar) and the local site pharmacist maintain records of the study drug delivery. Each participant is assigned a trial identity number, allocated at randomisation, for use on case report forms (CRF) and other trial documents, and the electronic database. All trial staff and investigators endeavor to protect the rights of the trial's participants to privacy and informed consent and adhere to the Data Protection Act, 1998. CRFs are held securely, in a locked room, or locked cupboard or cabinet.

**4.4. Trial Conduct and Audit.** Trial conduct is subject to audit of the Trial Master File. Entries on CRFs are verified by inspection against the source data. A sample of CRFs (10%) is 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 audited. Where corrections are required these will be subject to a full audit trail and justification.

**Trial Status.** RIGHT started recruiting patients in February 2010. Seventy-eight paramedics across 12 ambulance stations were trained over the trial period to recruit patients. The trial closed recruitment in December 2011 after 41 patients were recruited and final followup was in March 2012. The results will be submitted for publication later in 2012.

## 5. Discussion

The efficacy of thrombolysis with alteplase, the only licensed treatment for AIS, is time dependent and most effective if given within 3 hours [2]. Trials of putative neuroprotectant, for example, magnesium and NXY-059, have failed universally. This may be because these drugs simply don't work; however the relatively long time windows for inclusion of up to 6 or 12 hours may have contributed [4, 33]. Randomised controlled trials of managing physiological disturbances in acute stroke such as blood glucose and blood pressure have not yet shown any benefit, but again they had long time windows for recruitment [34, 35]. Hence, it is possible that neuroprotection and physiological management may also be time dependent and that these would be effective if given within a few hours, as with alteplase [2]. Unlike interventions that alter haemostasis, treatments that correct physiological disturbances may be started before the patient reaches the hospital prior to neuroimaging. However, no data are available on the practicality, logistics, diagnostic accuracy, and consent issues of performing trials in the UK ambulance environment in patients with ultra-acute stroke. This contrasts with the USA where ultra-acute administration of magnesium has been reported in a small uncontrolled study [4]; the large FAST-Mag trial is ongoing and Germany where mobile stroke units reduce treatment times in acute stroke patients [7].

The RIGHT study is assessing the feasibility of doing ambulance based stroke trials in the UK. Our process of proxy consent by the paramedics is novel and has not been used previously. While this may not be standard practice, it is vital to include patients with a range of clinical presentations,

including those with severe stroke, dysphasia, or reduced consciousness; indeed it is the right of such patients to be offered ultra acute treatment in the field. However, to ensure validity of the consent process, such patients can only be recruited provided another paramedic or technician acts as a witness to the consent procedure.

The RIGHT trial will also provide important information on the effects of GTN on haemodynamic variables in ultra-acute stroke. The study, including the nested qualitative work, will inform trial design for future larger randomised controlled trials assessing efficacy of interventions correcting physiological disturbances and neuroprotection in ultra-acute stroke. A multicentre trial of transdermal GTN in ultra-acute stroke is already in design, subject to the findings of RIGHT.

## Abbreviations

AIS:	Acute ischaemic stroke
BP:	Blood pressure
CBF:	Cerebral blood flow
EMAS:	East Midlands Ambulance Service
CRF:	Case report form
ENOS:	Efficacy of nitric oxide in stroke
FAST:	Face arm speech test
FAST-MAG:	Field administration of stroke therapy-magnesium phase 3 clinical trial
GCP:	Good clinical practice
INTERACT-2:	Intensive blood pressure reduction in acute cerebral haemorrhage trial-2
IMP:	Investigational medicinal product
MHRA:	Medicines and Health Regulatory Authority
mRS:	Modified rankin scale
NHS:	National Health Service
NUH:	Nottingham University Hospitals
PICH:	Primary intracerebral haemorrhage
RIGHT:	Rapid intervention with glyceryl trinitrate in hypertensive stroke
GTN:	Glyceryl trinitrate
SAE:	Serious adverse events
SUSAR:	Sudden unexpected serious adverse reaction
SSS:	Scandinavian stroke scale
ZDI:	Zung depression index.

## Conflict of Interests

P. M. W. Bath is the Chief Investigator of the ENOS trial. No other conflict of interests.

## Authors' Contribution

S. Ankolekar drafted the paper and contributed to the writing of the study protocol, obtaining study approvals, designing the case report forms, and training the paramedics. G. Sare and C. Geeganage helped with writing the initial study protocol and obtaining approvals. M. Fuller contributed to



the training of paramedics. L. Stokes, N. Sprigg, R. Parry, A. N. Siriwardena, P. M. W. Bath contributed to the study design and commented on the drafts of the paper. PB is the Chief Investigator.

## Acknowledgments

The authors thank the paramedics of EMAS, patients who are taking part in the RIGHT study. Stroke Research Nurses at the Division of Stroke, University of Nottingham for collecting the data, Consultant Stroke Physicians at the City Hospital for facilitating the trial, Sheila Hodgson and Rosie Roberts from the Clinical Trials Pharmacy at the Nottingham City Hospital for helping with the pharmacy arrangements. RIGHT is funded by the Nottingham University Hospitals NHS Trust R and D Pump Priming competition, and by the Division of Stroke. S. Ankolekar is funded by the UK Medical Research Council (Grant G0501797). P. M. W. Bath is The Stroke Association Professor of Stroke Medicine.

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