Rapid Intervention with GTN in Hypertensive stroke Trial (RIGHT)

Determining the potential of ambulance-based randomised controlled trials in patients with hyperacute stroke; assessment of glyceryl trinitrate in lowering blood pressure.

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STUDY SYNOPSIS

Title	Determining the potential of ambulance-based randomised controlled trials in patients with hyperacute stroke: assessment of glyceryl trinitrate in lowering blood pressure.
Acronym	RIGHT
Short Title	**R**apid **I**ntervention with **G**TN in **H**ypertensive Stroke **T**rial.
Chief Investigator	Professor Philip Bath.
Study Centre(s)	East Midlands Ambulance Service and the University of Nottingham.
Objectives	Primary: To determine the feasibility of using the ambulance service to investigate acute treatments for stroke. Secondary: To determine the effects of GTN on blood pressure, pulse pressure and rate pressure product on hypertensive stroke patients.
Methodology	Randomised, single blind study.
Number of participants	80.
Diagnosis and main criteria for inclusion	Positive FAST test Systolic Blood Pressure > 140.
Investigational treatments	Feasibility of performing a stroke trial in an ambulance. Transdermal glyceryl trinitrate.
Duration of treatment	90 days.
Reference therapy	No patch.
Criteria for safety	Death, neurological deterioration, dependency and stroke recurrence.
Statistical methods	Tabulation analysis for ambulance data. Comparison of GTN versus control

CONTENTS

ABBREVIATIONS

A&E	Accident and Emergency
AIS	Acute Ischaemic Stroke
BP	Blood Pressure
CBF	Cerebral Blood Flow
CHHIPS	Controlling Hypertension and Hypotension Immediately Post-Stroke
CIOMS	Council for International Organisation of Medical Sciences
COSSACS	Continue Or Stop post-Stroke Antihypertensives Collaborative Study
CRF	Case Report Forms
CT	Computer Axial Tomographic Scan
CVD	Cerebrovascular Disease
DoSM	Division of Stroke Medicine
ECG	Electrocardiogram
ED	Emergency Department
EMAS	East Midlands Ambulance Service
ENOS	Efficacy of Nitric Oxide in Stroke
FAST-MAG	Field Administration of Stroke Therapy-Magnesium
GCS	Glasgow Coma Scale
GTN	Glyceryl trinitrate
HR	Heart Rate
INTERACT	Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage-Trial
IMP	Investigational Medicinal Product
MHRA	Medicines and Health Care Products Regulatory Agency
MI	Myocardial Infarction
MMSE	Mini-Mental State Examination
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NCH	Nottingham City Hospital
NHS	National Institute of Health Service
NIH	National Institute of Health
NINDS	National Institute of Neurological Diseases and Stroke
PICH	Primary Intracerebral Haemorrhage
PP	Pulse Pressure
QMC	Queens Medical Centre
R&D	Research and Development
REC	Research Ethics Committee
RPP	Rate Pressure Product
SAE	Serious Adverse Event
SCAST	Scandinavian Candesartan Acute Stroke Trial
SSS	Scandinavian Stroke Scale
SUSAR	Sudden Unexpected Serious Adverse Reaction
TIA	Transient Ischaemic Attack

1 SUMMARY

Time from acute stroke event to enrolment in clinical trials needs to be reduced to improve the chances of finding effective treatments. No randomised trials of ambulance-based treatment have been reported in acute stroke and the practicalities of recruiting, consenting and treating patients are unknown. High blood pressure is common in acute stroke and associated independently with a poor outcome. We will perform a randomised controlled trial of transdermal glyceryl trinitrate in 80 patients with hyperacute stroke (≤4 hours of onset) with initial consent, randomisation and treatment being performed by paramedics in the ambulance. The trial will primarily assess the feasibility and logistics of running such a trial in the NHS ambulance service thereby providing a model for use in future hyperacute stroke studies; a secondary aim is to generate novel data on the effect of GTN on BP in the hyperacute setting.

2 BACKGROUND

Finding acute interventions which reduce early brain damage and improve outcome from acute stroke is of major importance and has proved challenging, e.g. aspirin has wide utility but modest efficacy, and alteplase the converse.[1] Anticoagulation has proved ineffective and neuroprotection approaches remain unproven.

Ambulance administration of emergency treatment is standard in acute medical emergencies, including myocardial infarction (MI: aspirin, thrombolysis) and acute asthma (bronchodilators, oxygen). Such treatments need standard diagnostic criteria thereby allowing an accurate initial diagnosis to be made (e.g. clinical presentation and ECG for MI); ambulance-administered treatment then needs to be tested in clinical trials. Hence, thrombolysis for MI was given 45 minutes earlier if administered in an ambulance than at hospital.[2] Treatments for acute ischaemic stroke (AIS) are not routinely administered prior to hospital since current therapies alter haemostasis (e.g. aspirin, alteplase) and need prior CT/MRI scanning to exclude primary intracerebral haemorrhage (PICH). However, other potential treatments for acute stroke such as neuroprotection and management of physiological disequilibrium (e.g. high blood pressure [BP], hyperglycaemia, pyrexia) do not necessarily need prior neuroimaging and could be delivered prior to hospitalisation. Any benefits of such interventions are likely to be highly time dependent so that pre-hospital administration could considerably increase treatment efficacy through reducing onset to treatment times. A recent study (FASTMag pilot) by Saver in Los Angeles of ambulance administration of intravenous magnesium (a potential neuroprotectant [3]) 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).[4] The main FASTMag trial (PI: JS, http://www.fastmag.info/) is now running in 1,298 pre-hospital patients from Los Angeles and is funded by NIH/NINDS. The trial has recruited 274 patients to date: mean age 62 years, AIS 71%, TIA 2%, PICH 27%. However, no ambulance-based trials involving stroke patients have been performed in the UK, and studies are needed in pre-hospital stroke care, as highlighted at a European Commission Workshop in 2005.[5]

Recently, Ford, Jenkinson and colleagues developed a standardised and validated diagnostic tool, the 'Face Arm Speech Test' (FAST), for use by paramedical staff in the initial diagnosis of acute stroke; the Joint Royal Colleges Ambulance Liaison Committee (JRCALC) have now adopted this as the national ambulance recognition instrument.[6, 7] Paramedics from the East Midlands Ambulance Service (EMAS) have used FAST since 2002 to deliver patients with probable acute CVD to the nearest acute hospital, Nottingham City Hospital (NCH) or Queen's Medical Centre (QMC), rather than always to A&E at QMC. Those patients destined for NCH are taken straight to the Acute Stroke Unit bypassing the NCH Emergency Assessment Unit, not least to aid with the rapid delivery of interventions such as thrombolysis. Hence, FAST is already being used as a triage, diagnostic and management tool in patients with acute stroke.

If we are to effectively test the ambulance service in its ability to participate in randomized controlled trials we must test a suitable treatment. In this study we propose using blood pressure treatments.

High blood pressure (BP>140/90 mmHg) is common in AIS and PICH, and independently associated with a poor outcome. [8-10] These observational data imply that lowering an elevated BP could improve outcome in both AIS and PICH, providing cerebral blood flow (CBF) is not reduced in the presence of dysfunctional autoregulation. This equipoise mean that physicians caring for stroke patients remain uncertain as to whether BP should be lowered or not [11] and emphasizes the need for trials of the effects of lowering BP acutely. 5 non-commercial multicentre trials are ongoing: CHHIPS (iv labetalol; po lisinopril, http://www.le.ac.uk/cv/research/CHHIPS/HomePage.html),[12] COSSACS(http://www.le.ac.uk/cv/research/COSSACS/COSSACShome.html),[13] ENOS (transdermal glyceryl trinitrate [GTN]; continue or stop prior antihypertensive therapy, www.enos.ac.uk/),[14] INTERACT ('usual' po/iv anti-hypertensive therapy, PICH only, http://www.thegeorgeinstitute.org/research/neurological-&-mental-health/studies-&-trials/) and SCAST (po candesartan, www.scast.no/). These trials are all hospital-based and therefore rarely recruit patients during the first 2-3 hours post ictus so that the effect of treatment timing on safety and efficacy is difficult to assess. Additionally, 30-40% of patients with acute stroke are dysphagic [15] so that oral treatment may be delayed or problematic (nasogastric tubes are often not tolerated; modified-release/slow-release preparations cannot be used since their pharmacokinetics are altered by crushing for insertion down the tube). Administration of treatment prior to hospital, e.g. 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. it does not require a formal swallowing assessment or oral administration of treatment).

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.[16-18] Nitric oxide is a candidate treatment for stroke being a key endogenous regulator of cerebral blood flow and tissue perfusion (CBF, probably through modulating pial vessel tone thereby potentially improving collateral blood flow) and has neuroprotective properties in experimental stroke.[19] Further, plasma NO levels (nitrate/nitrite) are low in acute stroke and associated with a poor outcome [20, 21] so supplementing NO in stroke might restore its normal functions. Importantly, GTN is recommended in management guidelines for BP management, especially in the context of controlling BP during thrombolysis (e.g. NIH NINDS t-PA trial [22]), albeit without good supporting safety data.[23]Evidence is increasing that peripheral systolic and diastolic BP measurements may not be the only haemodynamic estimates of vascular risk. Other measures, including central BP, pulse pressure (PP = systolic BP - diastolic BP), heart rate, rate-pressure product (RPP = systolic BP x heart rate), aortic compliance and pulse wave velocity have each been assessed and appear to be associated with vascular risk and outcome[24-29] GTN is a good candidate for use as the IMP in this trial as we have conducted several clinical trials in acute stroke using GTN and therefore have good safety data. GTN lowered 24 hour ambulatory BP (by 7%/5%),[16, 17] peripheral BP (by 12%/4%) and central BP (by 13%/4%) at 1 hour;[18] reductions which are well within the <20% recommended by experts in the absence of large trial data.[30] Additionally, GTN lowered pulse pressure (HR),rate-pressure product (RPP, non-significant trend) and aortic compliance, as assessed by the augmentation index on pulse wave analysis.[17, 31] GTN did not alter platelet function (aggregation, activation, and therefore may be given to patients with PICH,[16] in contrast to other nitric oxide donors such as sodium nitroprusside [32]), regional CBF (assessed using xenon CT) or middle cerebral artery blood flow velocity or pulsatility index; and did not induce cerebral steal or change cerebral perfusion pressure.[18] GTN appeared to be safe across the three GTN phase II trials (n=145) [16-18, 33]. However the effects of GTN on central BP and aortic compliance in the hyperacute stage of stroke is unknown. Central BP and aortic compliance (assessed as augmentation index, [AI]) may be measured non-invasively using the Sphygmocor device and the technique can detect drug-induced changes[27].

The safety and efficacy of GTN is now being tested in the ongoing 5,000 patient MRC-funded

'Efficacy of Nitric Oxide in Stroke (ENOS) trial (www.enos.ac.uk/), which is also comparing the effect of continuing vs. temporarily stopping prior antihypertensive therapy.[14] ENOS has recruited >1000 patients (as of 30/7/08). The independent Data Monitoring & Ethics Committee (DMEC) regularly review (6 monthly) the ENOS safety data and have no concerns about the ongoing trial.[34]

We propose to assess the feasibility of performing an ambulance-based trial in patients with hyperacute stroke, a key question for the future testing of potential interventions aimed at neuroprotection and physiological control. We will assess the effect of GTN on BP in this setting; GTN is an ideal treatment to assess in an ambulance-based trial since the drug is widely available and inexpensive, is easy to administer, and can be given to neuroprotect patients with either AIS or PICH (so no prior scanning is needed), and those with dysphagia. EMAS paramedics already use GTN patches in patients with stroke who develop concurrent angina or who are peripherally shutdown and need IV access (a GTN patch is placed over a vein to induce 'local' vasodilatation).

3 STUDY OBJECTIVES AND PURPOSE

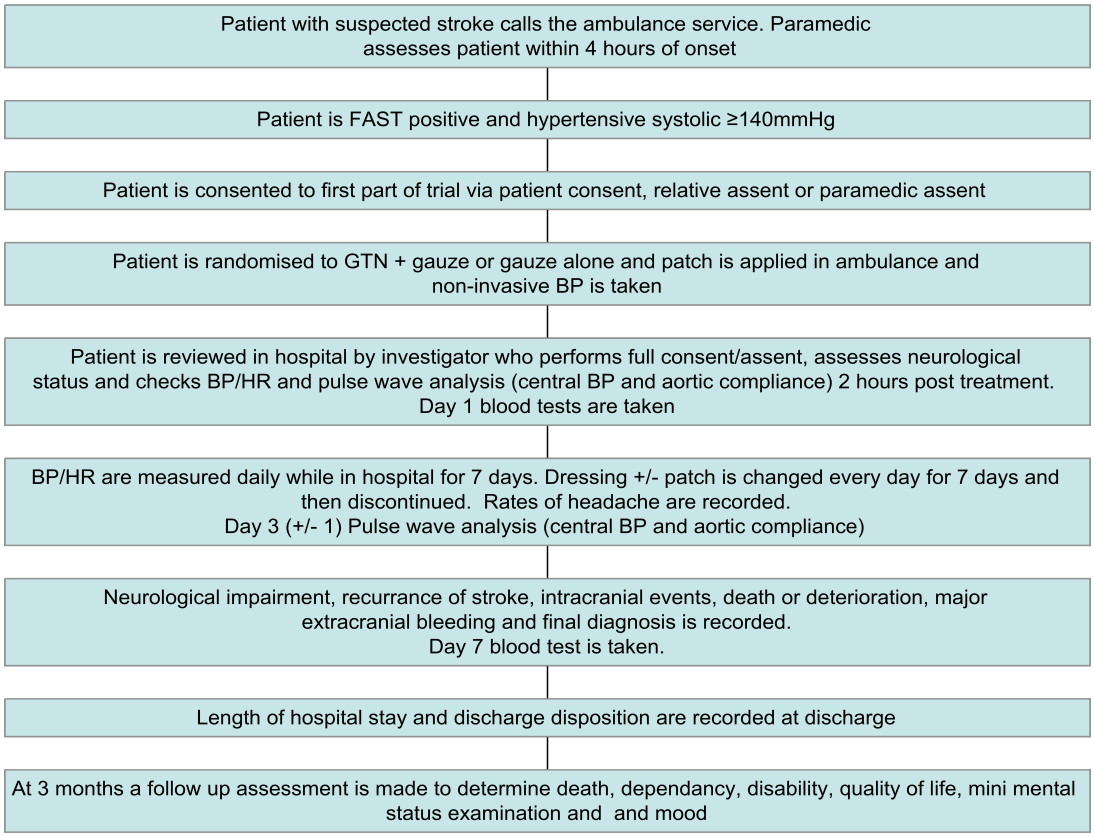
3.1 PRIMARY AIM

To assess the feasibility of using the ambulance service to test and deliver treatment for stroke in the hyperacute setting:

3.2 SECONDARY AIMS:

To assess the effects of GTN on central and peripheral blood pressure, central and peripheral pulse pressure (PP), rate pressure product (RPP), aortic compliance and surrogate markers of efficacy in blood in the hyperacute setting

4 TRIAL OVERVIEW



5 STUDY DESIGN

Ambulance-based, single city, single-blind, randomised controlled trial with blinded outcome assessment.

5.1 DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT

The GTN will given in the form of Nitro-Dur 0.2mg/hr, Schering-Plough Ltd.

5.1.1 Product Characteristics

Transdermal GTN is a licensed product and a summary of the product characteristics is available for investigators.

5.1.2 Supply, packaging and labelling

Standard NHS supplies will be used.

5.1.3 Storage, dispensing and return

GTN patched will be dispensed by NCH pharmacy. Each ambulance will carry two numbered opaque sealed envelope containing a gauze dressing +/- GTN patch, according to a computer-defined sequence. Paramedics will take study medications onto the ambulance at the beginning of their shift (as they do with opiates and cardiac thrombolytics). At the start of the trial the following 6 GTN patches for each patient will be dispensed by pharmacy and kept in the drug safe within the DoSM. These will be logged with batch number and expiry recorded when they are given to patients.

5.1.4 Placebo

There is no placebo treatment in this trial which is single blind only. Patients randomised to control will have a gauze dressing changed each day to blind them as to their treatment allocation

5.2 DESCRIPTION AND RATIONALE OF THE STUDY DESIGN

5.2.1 Interventions

The only intervention is Transdermal GTN 5mg or control. All other stroke treatment will be as per usual care.

5.2.2 Design Paradigm

Since the primary aim of the study is to test the consent and enrolment of patients into a clinical study within the pre-hospital phase of acute stroke, it might be argued that patients should not be randomised to an experimental treatment. Use of existing/standard treatments (such as fluids or oxygen) does not need consent. An experimental treatment could be given without randomised control therapy but this would not allow safety to be assessed adequately and it would miss the opportunity for gathering additional comparative information on GTN, e.g. safety and effect on BP. Further, ENOS has recruited few patients with hyperacute stroke so the proposed trial offers the chance to help address this limitation. Postponing enrolment until hospital admission will not address the primary question of exploring the feasibility of performing randomised controlled trials in ambulances. Additionally, it is not practical for assessing hyperacute effects of GTN on BP since although 25% patients reach hospital within 3 hours (and a further 25% over the next 3 hours),[35] enrolment into trials immediately after admission is fraught with delays related to the structure of A&E/EDs and acute stroke services. We believe the proposed plan allows two separate and important questions to be addressed within one trial.

5.2.3 Expected Value of Results

The issue of performing trials in the pre-hospital phase of stroke is critical if ictus-to-treatment times are to be reduced. Although pro- and anti-haemostatic agents (alteplase, anticoagulation, aspirin for AIS) could not be tested without prior neuroimaging, many other

potential treatments could, including those assessing neuroprotectants (as in FASTMag) and the management of physiological disequilibrium (e.g. BP [as here], glucose, oxygen, coma). Unfortunately, no data are available on the practicality, logistics (patient recruitment, paramedic involvement), diagnostic accuracy, and consent issues of performing trials in the UK ambulance environment in patients with hyperacute stroke; our study will provide vital information relevant to these questions. The data relating to GTN will provide further safety data for our programme of developing transdermal GTN as a treatment modality in acute stroke.

5.3 TRIAL SUBJECTS

5.3.1 Recruitment

Patients will be identified by trained paramedics crews participating in the trial. The paramedics will assess whether the patient is likely to have had a stroke using the validated Face Arm Speech Test (FAST), and ensure that other inclusion, exclusion criteria are met. Paramedics will then approach the patient/relative about participation in the trial, randomise a patient if consent/assent is gained and administer any trial medication. They will read out a brief pre-prepared sheet and the patient must decide if they are happy to enter the first stage of the trial. The first stage involves receiving a GTN patch or control in the ambulance and having a blood pressure taken. No further research activities would be carried out until further consent has been taken in the hospital. If the patient cannot give consent (stroke often causes communication problems) and relatives are available they would be able to consent on behalf of their relative. In addition, if no relative is available then the ambulance service will be able to recruit suitable patients into the first stage of the trial in the ambulance and relatives will be consulted when they are available for participation to continue.

5.3.2 Inclusion criteria:

- Adult male patients >40 years, female patient ≥55
- Paramedic assessment of stroke on basis of positive 'Face & Arm weakness & Speech abnormality Test (FAST)[6, 7] in the context of a call to a patient with a 'possible acute stroke' i.e FAST score of 2 or 3;
- Event ≤4 hours of onset (sleep stroke - onset as bed time);
- High systolic BP (≥140 mmHg).

5.3.3 Exclusion criteria

- No consent/assent is available
- GTN is indicated (e.g. concurrent angina)
- GTN is contraindicated (e.g. dehydration, hypovolaemia);
- Age male < 40 years, females <55 years;[36]
- Coma; GCS ≤8
- History of seizures[36]
- Non-ambulatory pre-morbidly (modified Rankin scale of >2)[36]
- Hypoglycaemia (if glucose tested).
- Clinical hypovolaemia (e.g. concurrent diarrhoea and/or vomiting, dry mucus membranes etc)
- Patients from a nursing home
- Patients who are pregnant or breast feeding

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

5.3.4 Consent/Assent

Verbal consent, relative assent or paramedic assent will take place in the ambulance. This will cover only the period in the ambulance will application of treatment and blood pressure measurement. Once the patient arrives in hospital a full patient or relative information sheet will be given and full informed written consent will be obtained from each patient; 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. Alternatively, assent 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.

5.3.5 Co-Enrolment in other trials

Concurrent uncoordinated co-enrollment of patients into two or more trials has the potential for introducing bias, 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 if they are already in another drug trial. Patients may subsequently be co-enrolled into non-drug trials.

5.3.6 Expected duration of subject participation

90 days

5.3.7 Removal of subjects 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. The subjects' physicians are not blinded to treatment allocation and can remove treatment if they feel it is clinically indicated.

5.4 TRIAL TREATMENT AND REGIMEN

Transdermal GTN (5 mg) or no patch in 80 patients. Subjects will be blinded to treatment by placement of a gauze dressing over the patch or a similar area of skin; single blinding will provide value for money whilst reducing bias. [Industry is unwilling to supply active and placebo patches.] GTN treatment will be continued in hospital for a total of 7 days (as per ENOS [14]). Treatment will be given on top of 'best hospital care', including alteplase (if appropriate) and multimodal secondary prevention. Pre-stroke antihypertensives will be continued or stopped according to the practice of the treating physician

5.4.1 Pulse Wave Analysis

Central systemic haemodynamics; central BP and aortic compliance will be assessed non invasively by applantation tonometry, using the Pulse Wave Analysis (PWA) system (Sphygmocor, Sydney, Australia). A tonometer with a Millar Micromanometer in its tip will be positioned on the skin over the maximal radial arterial pulsation in the left arm and pressed down on the artery against the underlying bone with the wrist in slight extension. Assessments will be done on Day 1 at 2 hours post randomisation and on Day 3(+/1).

The recorded radial artery pressure wave will be transformed to the corresponding central wave using the validated transfer function; augmentation index, a measure of systemic arterial stiffness, and central blood pressure are then derived automatically.

5.4.2 Screening assessments

The screening assessment will involve BP, FAST and the inclusion criteria.

5.4.3 Baseline data

Paramedics will collect clinical information using their standard proforma, including baseline Glasgow Coma Scale and BP, and BP 15 minutes following placement of the gauze/patch. In-ambulance management (monitoring, oxygen, fluids) will also be recorded. This information will be transcribed from paramedic form to the trial CRF in hospital. Further information will be collected in hospital: pre-morbid dependency (modified Rankin Scale, mRS); prior hypertension and medication(s); ischaemic heart disease; heart rate/rhythm (ECG); temperature; impairment (Scandinavian Stroke Scale, SSS); glucose; and blood urea/haematocrit (measures of dehydration).

5.4.4 Prior and concomitant treatments
All prior treatments may be continued at the discretion of the treating physician. All other stroke care in unaffected.

5.4.5 Follow Up
At the end of treatment (day 7 or earlier if discharged), hospital discharge/death (information on: CT scan, carotid duplex; acute treatment and secondary prevention); and day 90.

5.4.6 Blood Samples
Blood samples will be taken on two occasions during the trial. Baseline bloods will be taken after the patient has arrived in hospital and full consent/assent has taken place. A second blood test will be taken on day 4. Serum samples will be taken and centrifuged for 9 minutes at 7000 rpm and then may be frozen at -80C until analysis.

6 ADVERSE EVENTS

As GTN is a licensed, well-tested medication we will only collect serious adverse events in this trial.

6.1 SERIOUS ADVERSE EVENT:
A serious adverse event (SAE) is any adverse event occurring following study mandated procedures, having received the vaccine or placebo 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 jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

All adverse events will be assessed for seriousness, expectedness and causality:

6.1.1 Seriousness
The investigator will determine seriousness as per the criteria above and only record SAEs.

6.2 CAUSALITY

Unrelated or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration, that 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 SAE whose causal relationship to the study IMP is assessed by the Chief Investigator as "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.

6.3 RECORDING OF SERIOUS ADVERSE EVENTS

An SAE form will be completed for each individual SAE.

6.4 SUSAR

A serious adverse event that is sudden in its onset, unexpected in its severity and seriousness or is not a known side effect of the IMP and is 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 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, complete the CIOM 1 form and send to the MHRA.
- Shall, within a further eight days send any follow-up information and reports to the MHRA.
- Make any amendments as required to the study protocol and inform the ethics and regulatory authorities as required

6.5 SUBJECT REMOVAL FROM THE STUDY DUE TO ADVERSE EVENTS

Any subject who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

7 STATISTICAL DESIGN AND ANALYSIS

7.1 RANDOMISATION AND BLINDING

7.1.1 Randomisation:

Patients will be randomised using computer minimisation to ensure equal grouping of a priori baseline characteristics. The ratio of GTN to control is 1:1.

7.1.2 Blinding:

There is no placebo treatment in this trial, which is single blind only. Patients randomised to control will have gauze dressing changed each day to blind them as to their treatment allocation

7.2 DATA

7.2.1 Baseline data:

Paramedics will collect clinical information using their standard proforma, including baseline Glasgow Coma Scale and BP, BP 15 minutes following placement of the gauze dressing +/- GTN patch, in-ambulance management (monitoring, oxygen, fluids). This information will be transcribed from paramedic form to the trial CRF in hospital. Further information will be collected in hospital: pre-morbid dependency (modified Rankin Scale, mRS); prior hypertension and medication(s); ischaemic heart disease; heart rate/rhythm (ECG); temperature; impairment (Scandinavian Stroke Scale, SSS); glucose; and blood urea/haematocrit (measures of dehydration).

7.2.2 Follow-up:

At the end of treatment (day 7 or earlier if discharged), hospital discharge/death (information on: CT scan, carotid duplex; acute treatment and secondary prevention); and day 90.

7.3 OUTCOME MEASURES

7.3.1 Primary:

- Effects of GTN on BP at 2 hours post treatment. [This outcome represents the sum of the trial, i.e. ability to identify, recruit, randomise, treat, and make measurements in patients presumed stroke in an ambulance, and hand them over to hospital staff. The 2 hour time reflects the time to peak effect for GTN.]

7.3.2 Secondary:

Analyses will be performed in all patients (intention to treat) and those with confirmed stroke.

7.3.2.1 Ambulance trial logistics:

- Proportions of patients (i) randomised : approached about joining; (ii) randomised : carried in ambulance; and (iii) treated according to protocol : all randomised (= diagnostic accuracy); (iv) reasons for not enrolling (presence of exclusion criteria, refusal of consent).

7.3.2.2 Timings:

- Times from ictus to randomisation in ambulance; ictus to ED arrival, and randomisation to ED arrival.
- Paramedics: Interview on experience and views of consent and treatment; audit of routine care.
- Haemodynamic effects of GTN: on BP, HR and derivatives (PP, MAP, RPP) prior to ED arrival and at 2 hours. Central BP and aortic compliance will be assesed in both groups at 2 hours post randomisation and on Day 3(+/1).

7.3.2.3 In hospital:

- Scandinavian Stroke Scale at 2 hours; daily BP/HR/PP/RPP (BHS validated Omron 705CPII) over 7 days; rates of headache, hypotension/hypertension needing intervention.

7.3.2.4 Day 7:

- Death (cause); SSS; death/deterioration (day 7–0 SSS >5 points); recurrence-progression;[29] symptomatic intracranial events (haemorrhage, mass effect); major extracranial haemorrhage; final diagnosis (15-20% of patients with stroke mimics may be FAST positive).

7.3.2.5 At discharge/death:

- Length of stay in hospital; discharge disposition (death, institution, home).90 days: Death; death or dependency (mRS>2); disability (Barthel Index, BI<60); quality of life (EuroQoL); cognition (MMSE; mood (Zung; by face-to-face follow-up by blinded adjudicator.

7.3.2.6 Blood samples:

- To assess the effects of GTN on surrogate marker of efficacy (e.g. Serum S-100 protein).

7.4 POWER CALCULATION

Based on our previous clinical trials, and assuming a 14 (SD 14) mmHg reduction in BP with GTN at 2 hours with significance of 5% and randomisation 1 : 1 GTN : control, the sample size of 80 will provide >90% power. We believe this sample size is sufficient to provide convincing evidence on the utility and issues related to performing ambulance-based trials, and of assessing the effect of GTN on BP. This sample size will also give robust data on in-ambulance diagnostic and timing performance. We aim to enrol/randomise the 80 patients over 18 months (>1 patients/week), a feasible recruitment rate given the annual number of patients admitted to NUH. [Of note, the FASTMag pilot study recruited 20 patients.

7.5 ANALYSIS

Comparison by intention-to-treat of GTN versus no GTN, with adjustment for baseline value (by ANCOVA).

7.6 PROTECTION AGAINST BIAS

Bias will be reduced using multiple strategies: concealment of allocation; patient blinding to GTN (gauze pad over patch); measurements and follow-up blinded to treatment; assessment of patient recall of treatment;[17] exclusion of patients enrolled in other trials; analysis by intention-to-treat with adjustment for non-randomised treatment (e.g. aspirin, alteplase).

7.7 TIMELINES

Phase	0-2	3-19	20-24
Train ambulance/research staff	+		
Recruit patients		+	
Follow-up final patients			+
Present/write-up results			+

8 QUALITATIVE SUB STUDY

Key aspects of the feasibility of running ambulance based stroke trials, in the pre-hospital setting, may become apparent if we explore the experiences and challenges faced by the paramedics, who recruited or attempted to recruit to the study. Our pilot observations suggest that such challenges might include uncertainty in the diagnostic process, operational practicalities such as delay in the journey to the hospital, difficulties in discussing the trial with distressed patients and their relatives, and with patients who have impaired speech and comprehension. In this qualitative sub-study, we would like to explore such issues, in order to improve the design of future ambulance based stroke trials in the country.

8.1 AIM

To investigate the experiences, perceptions and challenges reported by paramedics in recruiting patients to an ambulance based hyper acute stroke trial.

8.2 DESIGN
Qualitative interview study with NHS staff.

8.3 PARTICIPANTS
Approximately 15 paramedics from the East Midlands Ambulance Service NHS Trust participating in the main study will be invited to take part. They will be informed about the sub study during the investigator meetings and by email. Contact details will be recorded for those who express an interest.

8.4 METHODS
The sub study will start midway into the main study after around 30 patients have been recruited. Paramedics, who have shown an interest and preferably have attempted to randomise at least one patient, will be contacted via telephone or email. From a practical perspective, and from our previous experience of conducting interview based studies in this professional group, [37, 38] a sample size of around 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 paramedics until no further new themes emerges. Details about the sub-study and what their participation will entail will be explained verbally to the paramedics; a written information sheet will also be given. Those who give informed consent will be interviewed.

8.5 DATA COLLECTION
Interviews will be carried out at the Clinical Sciences Building, University of Nottingham, City Hospital Campus Nottingham, in a room where disturbance is unlikely, at a time convenient to the participant. After rechecking consent, including permission to audio record the interview using a digital voice recorder, data will be collected using a semi-structured interview schedule as follows:

(Starting questions are in italics and follow up questions and probes are in bullet points)

a) *Can you recount for me the first time you attempted to randomise a patient into the trial?*
   - diagnosis, certainty
   - operational issues e.g. delay
   - consent issues – relatives, patients
   - paramedic's concerns, emotions

b) *For paramedics who have attempted to randomise just one more time, the same line of questioning will be followed with regards their second attempt, including asking about any differences.*

c) *For those who have attempted randomisation several times, after question 'a', ask:*
   - *What's been the best or easiest episode of attempting to randomise?*
   - *What's been the most difficult episode of attempting to randomise?*

d) *Were there things about the way that the trial was set up that need improving to help people like you with your part in it?*
   - *Method to distribute IMP to ambulance stations and paramedics*
   - *Written and verbal communication between paramedics and triallists*

e) *We are hoping to repeat this kind of trial. In an ideal world, what would be different about the design of it the next time around?*

f) *Are there some other issues that you had thought of which we haven't talked about yet?*

These questions will act as a guide only and the interviewer will seek to explore other relevant issues that participants raise. The interview will last approximately 60 minutes and where permission is not given to record digitally, handwritten notes will be taken.

8.6 DATA PROCESSING AND ANALYSIS

Digital voice recordings of each interview will be transferred to a password-protected folder on the investigators University computer. Transcripts will be anonymised, with pseudonyms used for personal and place names. Systematic, thematic content analysis, as described by Braun and Clarke [39] 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.

9 ETHICAL AND REGULATORY ASPECTS

9.1 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 instituted until the amendment and revised informed consent forms and participant and GP 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 implemented 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 and the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments.

9.2 DATA MONITORING COMMITTEE

A data monitoring committee (comprising Professor Peter Sandercock - Edinburgh, Dr Henning Mast – Associate Professor in Nottingham) will assess BP and safety data (death, impairment, dependency) when 20 and 40 patients have been recruited and had 7 days of follow-up. Ms Laura Gray (Medical Statistician) will prepare data for the committee.

9.3 INFORMED CONSENT AND PARTICIPANT INFORMATION

The initial approach will be from a member of the ambulance service

The investigator will inform the participant or their nominated representative (other individual or other body with appropriate jurisdiction), of all aspects pertaining to participation in the study.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial, the participant information sheets, and consent forms, but the consent

forms and information sheets will not be available printed in other languages. However, in this trial as the first stage of consent is in the ambulance an independent interpreter is unlikely to be available.

The process for obtaining participant informed consent or assent and parent / guardian informed 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 must both sign and date the Informed Consent Form before the person can participate in the study. If the patient can consent but not sign (due to stroke) witnessed consent is allowed.

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.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize 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).

9.4 SERVICE USER INVOLVMENT

NHS Paramedics from East Midlands Ambulance Service will initiate consent and treatment. In hospital trial procedures will be performed by the research staff funded by this grant. The Nottingham Stroke Patients forum discussed and supported the trial on 11/1/2006 and would be willing to take part if affected with a further stroke. The trial has been presented to, and is supported by, the EMAS board.

9.5 RECORDS

9.5.1 Drug accountability

Drug supplies will be dispensed from pharmacy at the start of the trial and kept in the DoSM drug safe. Temperature shall be monitored in the room where the medicines are kept. GTN patches will be allocated to randomisation envelopes to be kept securely in the ambulance.

The investigator and the local site pharmacist shall maintain records of the study drug's delivery to the pharmacy, an inventory at the site, the distribution to each participant, and the return to the 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 and bottles received by the pharmacy shall be accounted for.

9.5.2 Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomisation, for use on CRF's, other trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mm/yy).

CRF's 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 case additional follow-up is required.

CRFs shall be restricted to those personnel approved by the Chief Investigator and recorded on the 'Trial Delegation Log.'

CRFs are used to record clinical trial data and are an integral part of the trial and subsequent reports. The CRFs, therefore, must be legible and complete. 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 investigator shall sign the CRF to confirm the accuracy of the data recorded.

9.5.3 Source documents

Source documents provide evidence for the existence of the participant and permit verification of the data collected. 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.

9.5.4 Direct access to source data / documents

Direct access when required to the CRF and all source documents and other trial documentation e.g. signed consent forms, for the purpose of trial monitoring and audit and other lawful regulatory inspection.

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

9.6 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 will only collect the minimum required information for the purposes of the trial. 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 data base will be held securely and password protected.

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.

9.7 DATA SHARING AND PRESERVATION STATEGY

Anonymised data will be documented and shared (agreements already exist) with: the prospective 'Acute Blood Pressure Management Consortium' (CHHIPS, COSSACS, ENOS, INTERACT, SCAST); Cochrane 'Blood pressure in Stroke Collaboration' (BASC);[40, 41] and other researchers (assessed case-by-case). Since GTN patches are sourced from the NUH pharmacy, we have no commercial agreements or partnerships with pharma and no intellectual property is likely to result from the trial.

10 QUALITY ASSURANCE & AUDIT

10.1 COMPLIANCE

Transdermal GTN is easy to administer, including to dysphagic or semiconscious patients; compliance can be checked visually. GTN can cause headaches leading to patient withdrawal; the incidence of headache was low in our pilot studies and averages 9.3% over the ENOS trial start-up phase (but has led to few discontinuations). 85% of patients in ENOS have received ≥4 days of GTN/control.

10.2 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 indemnity arrangements for non-negligent harm and there are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures

Ongoing local monitoring and audit of the trial, its conduct and the data collected shall be carried out by the Trial Coordinator, or where required, a nominated designee of the Sponsor.

10.3 TRIAL CONDUCT

Trial conduct will be subject to 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.

10.4 TRIAL DATA

Audit 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.

10.5 QUALITY CONTROL OF DATA

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10%) 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 audited. Where corrections are required these will carry a full audit trail and justification.

10.6 RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines and regulations, the Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 5 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.

10.7 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.

10.8 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.

11 PUBLICATION AND DISSEMINATION POLICY

Study results may be published in peer-reviewed journals or presented at local, national or international scientific meetings.

Written reports from the qualitative research study will be produced for dissemination and publication (audiences – include the actual participants). These will not include details that would result in disclosure of individual paramedics' and patients' identities

12 STUDY FINANCES

12.1 FUNDING SOURCE

This Division of Stroke Medicine is seeking funding for this trial

12.2 PARTICIPANT STIPENDS AND PAYMENTS

Participants will not be paid to participate in the trial. Travel expenses will be offered for any hospital visits in excess of usual care.

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