APPLICANT'S CHECKLIST

CTIMP (Clinical trial of an investigational medicinal product)

REC Ref:	09/H0408/5	EudraCT No:	2007−004766−40
Short Title of Study:	RIGHT Trial		
CI Name:	Prof Philip Bath		
Sponsor:	University of Nottingham		

Please complete this checklist and send it with your application

- Send ONE copy of each document (except where stated)
- ALL accompanying documents must bear version numbers and dates (except where stated)
- When collating please do NOT staple documents as they will need to be photocopied.

Document	Enclosed?	Date	Version	Office use
Covering letter on headed paper	○ Yes ○ No			
NHS REC Application Form, Parts A&B	Mandatory			
Site−Specific Information Form (for SSA)	○ Yes ○ No			
Request form for authorisation from the MHRA (Annex 1 to ENTR/CT1) without enclosures	Mandatory			
Research protocol (6 copies)	Mandatory			
Investigator's brochure (3 copies)	○ Yes ○ No			
Summary C.V. for Chief Investigator (CI)	Mandatory			
Research participant information sheet (PIS)	Mandatory			
Research participant consent form	Mandatory			
Letters of invitation to participants	○ Yes ○ No			
GP/Consultant information sheets or letters	Mandatory			
Evidence of insurance or indemnity (non−NHS sponsors only)	Mandatory			
Letter from sponsor	○ Yes ○ No			
Letter from statistician	○ Yes ○ No			
Letter from funder	○ Yes ○ No			
Referees' or other scientific critique report	○ Yes ○ No			
Summary, synopsis or diagram (flowchart) of protocol in non−technical language	○ Yes ○ No			
Details of any Data Monitoring Committee	○ Yes ○ No			
Sample diary card/patient card	○ Yes ○ No			
Validated questionnaire	○ Yes ○ No			
Non−validated questionnaire	○ Yes ○ No			
Copies of advertisement material for research participants, e.g. posters, newspaper adverts, website. For video or audio cassettes, please also provide the printed script.	○ Yes ○ No			

WELCOME TO THE NHS RESEARCH ETHICS COMMITTEE APPLICATION FORM

An application form specific to your project will be created from the answers you give to the following questions.

1. Is your project an audit or service evaluation?

○ Yes ◉ No

2. Select one research category from the list below:

◉ Clinical trials of investigational medicinal products
○ Clinical investigations or other studies of medical devices
○ Other clinical trial or clinical investigation
○ Research administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
○ Research involving qualitative methods only
○ Research limited to working with human tissue samples and/or data
○ Research tissue bank

If your work does not fit any of these categories, select the option below:

○ Other research

2a. Please answer the following questions:

Is this trial subject to advice from the Expert Advisory Group on Clinical Trials and the Commission on Human Medicine prior to authorisation from MHRA?	○ Yes	◉ No

2b . Please answer the following questions:

a) Does the study involve the use of any ionising radiation?	○ Yes	◉ No
b) Will you be taking new human tissue samples?	◉ Yes	○ No
c) Will you be using existing human tissue samples?	○ Yes	◉ No

3. Is your research confined to one site?

◉ Yes ○ No

4. Does your research involve work with prisoners?

○ Yes ◉ No

5. Do you plan to include in this research adults unable to consent for themselves through physical or mental incapacity?

◉ Yes ○ No

5a. In which countries of the UK will the research sites be located? *(Tick all that apply)*

- [x] England
- [ ] Wales
- [ ] Scotland
- [ ] Northern Ireland

6. Is the study, or any part of the study, being undertaken as an educational project?

- ( ) Yes
- (•) No

NHS Research Ethics Committee NHS
Application form for a clinical trial of an investigational medicinal product

This form should be completed by the Chief Investigator, after reading the guidance notes. See glossary for clarification of different terms in the application form.

Short title and version number: (maximum 70 characters – this will be inserted as header on all forms)
RIGHT Trial

Name of NHS Research Ethics Committee to which application for ethical review is being made:
Nottingham 2

Project reference number from above REC: 09/H0408/5
Submission date: 23/12/2008

PART A: Introduction

A1. Title of the research

Full title: Determining the potential of ambulance–based randomised controlled trials in patients with hyperacute stroke; assessment of GTN in lowering blood pressure

Key words: stroke, ambulance, blood pressure

A2. Chief Investigator

Title:	Prof
Forename/Initials:	Philip
Surname:	Bath
Post:	Stroke Assocaitation Professor of Stroke Medicine
Qualifications:	MBBS, MD, FRCP, FRCPath
Organisation:	Univerisity of Nottingham
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	Clinical Sciences Building, City Hospital
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A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application

A3. Proposed study dates and duration

Start date: 01/02/2009
End date: 31/01/2011
Duration: Years: 2 ; Months: 0

A4. Primary purpose of the research: *(Tick as appropriate)*

- ☐ Commercial product development and/or licensing
- ☑ Publicly funded trial or scientific investigation
- ☐ Educational qualification
- ☐ Establishing a database/data storage facility
- ☐ Other

A5. Type of medicinal trial:

- ☐ Clinical trial of a non−authorised investigational medicinal product
- ☑ Clinical trial of an authorised product for a new indication, i.e. not in the Summary of Product Characteristics, (SmPC)
- ☐ Clinical trial of an authorised medicinal product in new conditions of use (different from those in the SmPC, i.e. new target population, new dosage schemes, new administration route, etc.)
- ☐ Clinical trial of an authorised medicinal product used according to the SmPC
- ☐ Other

If Other, please specify:

A5a. Phase of medicinal trial: *(Tick one category only)*

- ○ Human pharmacology trial *with no evidence of potential benefit to the proposed participants* (Phase 1 or 1/2a)
- ◉ Therapeutic exploratory trial in patients (Phase 2)
- ○ Therapeutic confirmatory trial in patients (Phase 3)
- ○ Therapeutic use trial in patients (Phase 4)

Applicants must enclose a copy of the completed request for authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA). The application form is published as Annex 1 to the European Commission guideline ENTR/CT1 and can be obtained from the EudraCT website at http://eudract.emea.eu.int.

A6. Does this research require site−specific assessment (SSA)? (Advice can be found in the guidance notes on this topic.)

◉ Yes ○ No

If No, please justify:

If Yes, an application for SSA should be made for each research site on the Site−Specific Information Form and submitted to the relevant local Research Ethics Committee. Do not apply for SSA at sites other than the lead site until the main application has been booked for review and validated by the main Research Ethics Committee.

Management approval to proceed with the research will be required from the R&D office for each NHS care organisation in which research procedures are undertaken. This applies whether or not the research is exempt from SSA. R&D applications in England, Wales and Scotland should be made using the Site−Specific Information Form.

PART A: Section 1

A7. What is the principal research question/objective? *(Must be in language comprehensible to a lay person.)*

The main objective of the trial is to determine whether it is possible to conduct a trial in stroke patients in the first few hours after onset by using the ambulance service to assess, consent, randomise and administer medication.

A8. What are the secondary research questions/objectives? *(If applicable, must be in language comprehensible to a lay person.)*

The secondary aim of the trial is to assess the effects of glyceryl trinitrate (GTN), a well established medication for the treatment of angina which also lowers blood pressure, on blood pressure and other measures in stroke patient with high blood pressure within 4 hours of onset. We will also examine surrogate markers of effectiveness using blood tests.

A9. What is the scientific justification for the research? What is the background? Why is this an area of importance?*(Must be in language comprehensible to a lay person.)*

Stroke is the third most common cause of death in the UK, 11% of all deaths. After the onset of a stroke there are several hours when areas of the brain are in danger of permanent damage but when medical intervention may help to prevent this. This would mean that treated patients have less long term disability after their stroke, and are less likely to die. It is, therefore, of increasing importance to identify and test treatments for stroke which can be delivered in this critical time period.

One of the major difficulties in achieving this is the time taken for patients to reach hospital after the onset of their stroke. By the time many patients reach hospital the time to save brain has often gone. Testing drugs which may save brain and improve outcome is therefore very difficult. One way of solving this would be to have the ambulance service initiate trials. If paramedics can correctly identify, consent, randomise and treat patients with acute stroke within a trial it would great assist our ability to test potential new drugs for the early stages of stroke.

In order to test whether it is possible for the ambulance service to be involved in trials, we need an intervention to test. In this trial we propose testing a drug that can lower blood pressure (BP) in acute stroke. We feel it is essential to test a real intervention, rather than conduct a 'sham' trial for the following reasons. The primary aim of this trial is to see if randomisation into stroke trials is possible using the paramedic service. If both the paramedics and patients know that the 'treatment' is inactive and therefore unable to cause side−effects etc, we have not truly tested the hypothesis; paramedics and patients alike may not treat this study as they would a true clinical trial of an IMP.

We believe that investigating a treatment for hypertension would be the most suitable option for several reasons. We know that patients who have high blood pressure after their stroke are more likely to die or be disabled than those with normal BP at this time. However, there is no current evidence to support early blood pressure lowering. It is possible to use GTN to lower blood pressure in stroke, and this would have several advantages in this situation. First, GTN has a been used for decades in the context of heart disease; GTN is safe and its side effects of the drug are well documented; second, it is available as a transdermal patch which can be easily administered even in patients who cannot swallow; third, paramedics are already allowed to admister transdermal GTN to aid intravenous access; and fourth, we have conducted extensive research into GTN use in acute stroke and we have robust information on the amount of blood pressure reduction that can be expected in stroke patients (about 10% systolic), and the potential adverse effects. We have conducted a study that showed it is possible to use GTN to reduce BP in acute stroke without harming cerebral blood flow. In addition, we are currently conducting an MRC funded international, multicentre trial (the ENOS trial) using GTN to treat high blood pressure within 48 hours of onset. This trial is due to complete in 2011. To date more than 1,000 patients have been recruited and only 20 patients have suffered from hypotension requiring intervention during treatment with GTN. To date there have been 177 adjudicated serious adverse events, of which only 2 have been definitely or probably related to GTN (both headache).

We feel that this is an important study and we hope you accept the suitability of GTN as a test treatment.

A10–1. Give a full summary of the purpose, design and methodology of the planned research, including a brief explanation of the theoretical framework that informs it. It should be clear exactly what will happen to the research participant, how many times and in what order.

This section must be completed in language comprehensible to the lay person. It must also be self–standing as it will be replicated in any applications for site–specific assessment on the Site–Specific Information Form. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.

Stroke is a devastating disease affecting about 120,000 people in the UK alone each year. While it is important to try and prevent strokes from occuring, it becoming clear that if action is taken early after the onset of a stroke death and disability can be prevented. There are already new drugs available for stroke that can reduce death and disability if given within 3 hours of onset of sypmtoms and there are more drugs currently being developed which may also help.

These new treatment work on the premise that in the first few hours after the onset of a stroke, some brain tissue is still alive and salvagable but in danger of permenant damage. Developing new treatments that can save brain and therefore prevent death and disability are key areas of research. However, it can be difficult to test these treatments in stroke patients to see if they work as there are only a few hours available after the onset of symptoms when they can be administered. By the time a patient reaches hospital, the usual site for recruitment and treatment in acute stroke trials, these hours are often past. Involving the ambulance service in the identification of suitable patients, the process of randomising patients to treatments and the administration of these treatments may allow treatments for acute stroke to be tested more successfully.

In this study we aim to test whether the ambulance service is able to correctly identify acute stroke patients, randomise them to a treatment (in this case a blood pressure treatment) and administer the first dose of the treatment within 4 hours of onset of symptoms.

In order to properly test whether the ambulance service can run a trial we need a drug to test and we propose using a blood pressure treatment. It is important to use a real treatment to test, as conducting a 'sham' trial would not truly test whether or not the paramedics can recruit and treat patients with real medication. High blood pressure is common in the first hours and days following a stroke and we know from studies that these patients are more likely not to recover fully and be left with some disability. At present, doctors do not routinely treat high blood pressure in these first hours and days after a stroke. Lowering blood pressure in this early stage after a stroke with medications might help patients to recover. This question is already being studied by a large international trial called the ENOS trial which recruit patients with high blood pressure up to 48 hours after the onset of stroke. However, in the ENOS trial few patients are included in the study within 4 hours of onset of their stroke because of the problems outlined above and therefore the treatment is not given at a time when it is most likely to be beneficial. In the RIGHT trial we want to use the same blood pressure lowering drug as the ENOS trial, Glyceryl Trinitrate or GTN (a along established much used drug to treat angina) to lower blood pressure. This drug has the advantage that is comes in a patch and can be given to all stroke patients even if the stroke has affected thier swallow. We also have considerable safety data on the use of GTN in acute stroke as we have randomised more than 1,000 patients into trials using GTN in acute stroke, and we know the side effect/complication rate to be very low.

The primary aim of this trial is to assess whether it is feasible to use the ambulance service to recruit stroke patients into clinical trials with 4 hours of the onset of their symptoms. Secondary information will be gained on the effects of GTN on blood pressure and other measures in patients with stroke.

Patients who have the symptoms of a stroke and who telephone for an ambulance will be assessed by the paramedics who come to their aid. The paramedics will confirm whether they are likely to have had a stroke by using an assessment designed for non–doctor heath care workers called the FAST test. This assesses whether a person has face or arm weakness or speech difficulty which are very common in stroke. The FAST test has been shown to be successful in identifying patients with stroke.

If the patients fits the criteria the paramedics will explain that if they wish they may enter the clinical trial. 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 blood pressures taken in the ambulance and for the first 24 hours in hospital. No further research activities would be carried out until further consent has been taken in the hospital. If the patient cannot consent for themselves (stroke aften 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.

The patient will then be randomised to receive either a GTN patch or no patch (the control). A preprapred envelope will be in each ambulance ready for use. Patients with no patch will have a gauze swab placed where the patch would be in order to try and hide which treatment they are receiving from them. The patient would have blood pressures taken 2 hours after the patch goes on and 1 extra blood pressure measurement every day for 7 days, which is the length of time they would be treated with the GTN/control. The patch and/or gauze swab is changed every day. After 7 days there are no more treatments in this trial.

Patients will have 2 blood tests during the course of the trial. The first will be on the first day after full consent or assent has been taken in hospital and the second will be on day 4. These will be examined for surrogate markers of stroke to see if treated patients do better than those that aren't treated.

Patients would have their disability level assessed by a nurse 1 week after their stroke (or sooner if they leave hospital sooner) and they would also have a telephone call after 3 months to see how they are. This phone call will ask how they are functioning physically as also perform short tests of memory, mood and quality of life.

All other treatments for stroke are exactly as they would normally be, including giving asprin, cholesterol tablets and other blood pressure tablets if required. Patients will be able to have physio and occupational therapy as normal. The trial involves no additional scans.

A10–2. In which parts of the research have patients, members of the public or service users been involved?

- ☐ As user–researchers
- ☐ As members of a research project group
- ☐ As advisor to a project
- ☐ As members of a departmental or other wider research strategy group
- ☑ None of the above

Please provide brief details if applicable:

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 East Midlands Ambulance Service board.

A10–3. Could the research lead to the development of a new product/process or the generation of intellectual property?

○ Yes ◉ No ○ Not sure

A11. Will any intervention or procedure, which would normally be considered a part of routine care, be withheld from the research participants?

○ Yes ◉ No

A12. Give details of any clinical intervention(s) or procedure(s) to be received by research participants over and above those which would normally be considered a part of routine clinical care. *(These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material.)*

Additional Intervention	**Average number per participant**		**Average time taken** (mins/hours/days)	**Details of additional intervention or procedure, who will undertake it, and what training they have received.**
	Routine Care	Research		
Other	0	7	2 minutes	Application of 5mg transdermal GTN patch if randomised to do so, or of a gause patch only if randoised to control. The study

				nurse or doctor will apply the patch.
Other		9	3 minutes	A non invasive blood pressure will be taken by the study nurse or doctor with an OMRON BP machine. Twice on the first day and then daily for 7 days.
Venepuncture		2	5 minutes	The research nurse or doctor will take blood on day 1 and day 4 of the trial. They will be trained in venopuncture according to hospital policy.

A13. Give details of any non−clinical research−related intervention(s) or procedure(s).*(These include interviews, non−clinical observations and use of questionnaires.)*

Additional Intervention	**Average number per participant**	**Average time taken** (mins/hours/days)	**Details of additional intervention or procedure, who will undertake it, and what training they have received.**
Face to Face Interview	1	30 mins	The interview will be carried out by a research nurse experienced in clinical trials and trained in GCP and the EU directive.

A14. Will individual or group interviews/questionnaires discuss any topics or issues that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could take place during the study (e.g. during interviews/group discussions, or use of screening tests for drugs)?

○ Yes ◉ No

The Information Sheet should make it clear under what circumstances action may be taken

A15. What is the expected total duration of participation in the study for each participant?

90 days

A16. What are the potential adverse effects, risks or hazards for research participants either from giving or withholding medications, devices, ionising radiation, or from other interventions (including non−clinical)?

There are scientific arguements which say that lowering blood pressure in acute stroke could be harmful, although there are also strong arguements that it could also be beneficial. The ENOS trial of GTN in acute stroke has treated > 700 patients to date and has not shown harm when the data is reviewed by the data monitoring committee and we conclude that the risk is small.

A17. What is the potential for pain, discomfort, distress, inconvenience or changes to lifestyle for research participants?

GTN can have the side effect of causing headache, although this is rarely bad enough to cause discontinuation of treatment. The GTN can can cause local irritation to the skin but this is usually mild and resolves when the patch is removed.

Blood tests may cause mild discomfort or bruising.

A18. What is the potential for benefit to research participants?

The primary outcome of assessing whether a randomised controlled trial can be carried out by the ambulance service will not directly benefit participants in the trial.

A19. What is the potential for adverse effects, risks or hazards, pain, discomfort, distress, or inconvenience to the researchers themselves? *(if any)*

There are none identified

A20. How will potential participants in the study be (i) identified, (ii) approached and (iii) recruited?
Give details for cases and controls separately if appropriate:

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. They will read a brief description of the trial to the patient/relative and gain consent assent to administer trial medication in the ambulance. When the patient arrives in hospital they will be given a full patient/relative information sheet and asked to consent to continued participation in the trial.

If the patient is unable to consent then we propose that the paramedics be able to enroll patients in the first stage of the trial and administer trial medication in the ambulance. Assent to continue in the trial will be gained once the patient is in hospital.

A21. Where research participants will be recruited via advertisement, give specific details.

☑ Not Applicable

If applicable, enclose a copy of the advertisement/radio script/website/video for television (with a version number and date).

A22. What are the principal inclusion criteria? *(Please justify)*

•Adult male patients >40 years, female patient ≥55
•Paramedic assessment of stroke on basis of positive 'Face & Arm weakness & Speech abnormality Test (FAST) in the context of a call to a patient with a 'possible acute stroke':ie FAST score ≥2.
•Event <4 hours of onset (sleep stroke – onset as bed time)
•High systolic BP (>140 mmHg).

The FAST assessment is a validated test designed to help non–physican medical profesionals accuratley identify stroke patients.
The 4 hour time window is to identify whether trial can be conducted within the amount of time necessary to prevent permenant brain loss in acute stroke
We need patients to have a high BP in order that they be suitable for blood pressure lowering treatment with GTN.

A23. What are the principal exclusion criteria? *(Please justify)*

•No consent/assent is available
•GTN is indicated (e.g. concurrent angina)
•GTN is contraindicated (e.g. dehydration, hypovolaemia);
•Age: male <40 years; women <55 years
•Coma; GCS ≤8
•History of seizures
•Non–ambulatory pre–morbidly (modified Rankin scale of >2)
•Hypoglycaemia (if glucose tested).

•Clinical hypovolaemia (e.g. concurrent diarrhoea and/or vomiting, drug mucus membranes etc)
•Patients from a nursing home
•Patients who are pregnant or breast feeding

It would not be possible for patients to enter the trial if they either need or cannot be randomised to a nitrate. The stroke screening test is appropriate only patients <40 as below this age non–stroke pathology is too likely. Women can only be included over the age of 55 to prevent pregnant women from being randomised, as there will not be time to perform a pregnancy test.
A history of seisures or hypoglycaemia means symtoms may not be due to stroke
We wish to examine whether more patients are independant after treatment than control, therefore they need to be ambulatory and independent prior to stroke onset.
GTN can occasionally cause larger than usual blood pressure falls if patients are hypovolaemic. Therefore hypovolaemic should be clinically excluded before randomisation.

A24. Will the participants be from any of the following groups? *(Tick as appropriate)*

- ☐ Children under 16
- ☐ Adults with learning disabilities
- ☐ Adults who are unconscious or very severely ill
- ☐ Adults who have a terminal illness
- ☑ Adults in emergency situations
- ☐ Adults with mental illness (particularly if detained under Mental Health Legislation)
- ☐ Adults with dementia
- ☐ Prisoners
- ☐ Young Offenders
- ☐ Adults in Scotland who are unable to consent for themselves
- ☐ Healthy Volunteers
- ☐ Those who could be considered to have a particularly dependent relationship with the investigator, e.g. those in care homes, medical students
- ☐ Other vulnerable groups

Justify their inclusion.

By definition a trial of acute stroke within 4 hours of onset must involve patients that are in an emergency situation. In order to potentially save brain cells from dying it is important to intervene at this time. The emergency situation and the nature of stroke as an illness means that the patients may not be able to give consent themselves to be included in the trial.

- ☐ No participants from any of the above groups

A25. Will any research participants be recruited who are involved in existing research or have recently been involved in any research prior to recruitment?

○ Yes ◉ No ○ Not Known

If Yes, give details and justify their inclusion. If Not Known, what steps will you take to find out?

A26. Will informed consent be obtained from the research participants?

◉ Yes ○ No

If Yes, give details of who will take consent and how it will be done. Give details of any particular steps to provide information (in addition to a written information sheet) e.g. videos, interactive material.

If participants are to be recruited from any of the potentially vulnerable groups listed in A24, give details of extra steps taken to assure their protection. Describe any arrangements to be made for obtaining consent from a legal representative.

If consent is not to be obtained, please explain why not.

For patients who can consent, consent will be gained. A brief description of the trial will be read to the patient in the ambulance and verbal consent will be taken for the patient to receive trial medication in the ambulance. Once in hospital a full patient information sheet will be given to the patient and an investigator will be available to answer questions. The hospital investigator will take written consent.

If a patient cannot consent and a relative is available verbal assent will be gained from the relative in the ambulance to receive study medication in the ambulance and written assent will be obained from the relative on behalf of the patient once in hospital. A relative information sheet will be given and the hospital investigator will be available to answer questions.

If no relative is available and the patient cannot give consent the paramedic would be able to get assent for emergency treatment over the telephone from a independent physician.

Copies of the written information and all other explanatory material should accompany this application.

A27. Will a signed record of consent be obtained?

◉ Yes ○ No

If Yes, attach a copy of the information sheet to be used, with a version number and date.

A28. How long will the participant have to decide whether to take part in the research?

The patient or their relative must respond immediately following the reading of the paramedic information sheet. Once in hospital they will have 1 hour to consider continuing in the study before written consent/assent is obtained.

A29. What arrangements have been made for participants who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? *(e.g. translation, use of interpreters etc.)*

In this emergency trial it is not practical to be able to provide paramedics who are able to speak other languages and as such we will not seek to recruit patients who cannot understand English sufficient to understand the trial.

A30. What arrangements are in place to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

If further information becomes available all participants will be contact and asked whether they wish to continue participation in the trial.

Question(s) 30–1 disabled.

A31. Does this study have or require approval of the Patient Information Advisory Group (PIAG) or other bodies with a similar remit?*(see the guidance notes)*

○ Yes ◉ No

A32a. Will the research participants' General Practitioner (and/or any other health professional responsible for their care) be informed that they are taking part in the study?

(●) Yes ( ) No

If Yes, enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A32b. Will permission be sought from the research participants to inform their GP or other health professional before this is done?

(●) Yes ( ) No

If No to either question, explain why not

It should be made clear in the patient information sheet if the research participant's GP/health professional will be informed.

A33. Will individual research participants receive any payments for taking part in this research?

( ) Yes (●) No

A34. Will individual research participants receive *reimbursement of expenses* or any other *incentives or benefits* for taking part in this research?

(●) Yes ( ) No

If Yes, indicate how much and on what basis this has been decided:

If a patient to be seen following discharge travel expenses will be reimbursed. However this is not expected as the follow up assessment will be done by a telephone call.

A35. Insurance/indemnity to meet potential legal liabilities

Note: References in this question to NHS indemnity schemes include equivalent schemes provided by Health and Personal Social Services (HPSS) in Northern Ireland.

A35–1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the *sponsor(s)* for harm to participants arising from the *management of the research*?

Note: Where a NHS organisation has agreed to act as the sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, describe the arrangements and provide evidence.

( ) NHS indemnity scheme will apply
(●) Other insurance or indemnity arrangements will apply (give details below)

The University of Nottingham provides insurance for its clinical trials.

Please enclose a copy of relevant documents.

A35–2. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the *sponsor(s) or employer(s)* for harm to participants arising from the *design of the research*?

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), describe the arrangements and provide evidence.

- ○ NHS indemnity scheme will apply to all protocol authors
- ◉ Other insurance or indemnity arrangements will apply (give details below)

The University of Nottingham is responsible for the trial design and maintains clinical trials insurance in the event of subsequent harm to participants.

Please enclose a copy of relevant documents.

A35–3. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of *investigators/collaborators* and, where applicable, *Site Management Organisations*, arising from harm to participants in the *conduct of the research*?

Note: Where the participants are NHS patients, indemnity is provided through NHS schemes or through professional indemnity. Indicate if this applies to the whole of the study (there is no need to provide documentary evidence). Where non–NHS sites are to be included in the research, including private practices, describe the arrangements which will be made at these sites and provide evidence.

- ◉ All participants will be recruited at NHS sites and NHS indemnity scheme or professional indemnity will apply
- ○ Research includes non–NHS sites (give details of insurance/indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A36. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

○ Yes ◉ No

If Yes, give details of the compensation policy:

Please enclose a copy of relevant documents.

A37. How is it intended the results of the study will be reported and disseminated? *(Tick as appropriate)*

- ☑ Peer reviewed scientific journals
- ☐ Internal report
- ☑ Conference presentation
- ☐ Other publication
- ☐ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ Written feedback to research participants
- ☐ Presentation to participants or relevant community groups
- ☐ Other/none e.g. Cochrane Review, University Library

A38. How will the results of research be made available to research participants and communities from which they are drawn?

Results will be available through the scientific literature.

A39. Will the research involve any of the following activities at any stage (including identification of potential research participants)? *(Tick as appropriate)*

- [x] Examination of medical records by those outside the NHS, or within the NHS by those who would not normally have access
- [ ] Electronic transfer by magnetic or optical media, e−mail or computer networks
- [ ] Sharing of data with other organisations
- [ ] Export of data outside the European Union
- [x] Use of personal addresses, postcodes, faxes, e−mails or telephone numbers
- [ ] Publication of direct quotations from respondents
- [ ] Publication of data that might allow identification of individuals
- [ ] Use of audio/visual recording devices
- [ ] Storage of personal data on any of the following:
  - [ ] Manual files including X−rays
  - [ ] NHS computers
  - [ ] Home or other personal computers
  - [x] University computers
  - [ ] Private company computers
  - [ ] Laptop computers

Further details:

Paramedics who would ordinarily have access to the patients medical information will identify patients and take consent. Only after the consent process will follow up visits will be performed by University staff with honourary NHS contracts who would not not normally have access to medical notes.

We require names and addresses so that follow up can be arranged.

A40. What measures have been put in place to ensure confidentiality of personal data? Give details of whether any encryption or other anonymisation procedures have been used and at what stage:

Confidential data on patients will be kept in locked filing cabinets within the Division of Stroke Medicine (DoSM) in the Clinical Sciences Building at City Hospital. No patient identifiable data will be available to anyone outside the DoSM and the data will only be used for trial purposes as laid out in the patient and relative information sheets.

A41. Where will the analysis of the data from the study take place and by whom will it be undertaken?

Analysis of the data will take place by investigators and statisticians within the Division of Stroke Medicine at the University of Nottingham

A42. Who will have control of and act as the custodian for the data generated by the study?

The chief investigator, Prof Philip Bath

A43. Who will have access to research participants' or potential research participants' health records or other personal information? *Where access is by individuals outside the normal clinical team, justify and say whether consent will be sought.*

Research investigators will have access to the patients usual medical records after the consent process. Other staff within the University of Nottingham will have access to the trial documents but not to the medical notes in order to collate and analyse information. Staff from the University of Nottingham Division of Stroke Medicine may conduct an audit of the trial to confirm the quality of the trial by comparing collected data with the patients medical notes. Consent will be sought for this.

A44. For how long will data from the study be stored?

7 Years Months

Give details of where they will be stored, who will have access and the custodial arrangements for the data:

Data will be stored in locked filing cabinets within the Clinical Sciences Building at Nottingham City Hospital.

A45–1. How has the scientific quality of the research been assessed? *(Tick as appropriate)*

- ☐ Independent external review
- ☐ Review within a company
- ☐ Review within a multi–centre research group
- ☑ Review within the Chief Investigator's institution or host organisation
- ☐ Review within the research team
- ☐ Review by educational supervisor
- ☐ Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

The protocol has been assessed by the University of Nottingham research innovations department in their role as sponsor.

A45–2. How have the statistical aspects of the research been reviewed? *(Tick as appropriate)*

- ☐ Review by independent statistician commissioned by funder or sponsor
- ☐ Other review by independent statistician
- ☐ Review by company statistician
- ☑ Review by a statistician within the Chief Investigator's institution
- ☐ Review by a statistician within the research team or multi–centre group
- ☐ Review by educational supervisor
- ☐ Other review by individual with relevant statistical expertise

In all cases give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

Title:	Forename/Initials:	Surname:
Miss	Laura	Gray

Department:	Division of Stroke Medicine
Institution:	Univerisity of Nottingham
Work Address:	Clinical Sciences Building City Hospital

	Nottingham
Postcode:	NG5 1PB
Telephone:	0115 8231772
Fax:	0115 8231771
Mobile:	
E–mail:	laura.gray@nottingham.ac.uk

Please enclose a copy of any available comments or reports from a statistician.

Question(s) 46–47 disabled.

A48. What is the primary outcome measure for the study?

•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.]

A49. What are the secondary outcome measures? *(if any)*

Analyses will be performed in all patients (intention to treat) and those with confirmed stroke.
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).
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.
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.
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).
At discharge/death:
•Length of stay in hospital; discharge disposition (death, institution, home).Three months: 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.
Blood samples:
•To assess the effects of GTN on surrogate marker of efficacy (e.g. Serum S–100 protein).

A50. How many participants will be recruited?
If there is more than one group, state how many participants will be recruited in each group. For international studies, say how many participants will be recruited in the UK and in total.

80

A51. How was the number of participants decided upon?

Since the primary aim of the study is qualitative by assess the feasibility of performing clinical trials in patients with acute stroke whilst being transported by ambulance to hospital, and no such previous trials have been performed in the UK, we have not performed a sample size calculation on this outcome. We aim to

enrol/randomise 80 patients over 18 months (>1 patients/week), a feasible recruitment rate given the annual number of patients admitted to NUH.

If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.

Based on our previous clinical trials, the sample size of 80 will provide >90% power for detecting a 14 (SD 14) mmHg reduction in BP with GTN (assuming significance of 5% and randomisation 1 : 1 GTN : control). 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 in the hyperacute setting.

A52. Will participants be allocated to groups at random?

(•) Yes ( ) No

If yes, give details of the intended method of randomisation:

Paramedic investigators will have a pre−assigned randomised envelope in the ambulance which they will open once the patient is in the trial. Allocation of treatment in these envelopes will be randomised.

A53. Describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

Primary outcome will be evaluated using tabulation of ambulance parameters and haemodynamic parameters. Secondary outcome will be evaluated by comparison by intention−to−treat of GTN versus no GTN, with adjustment for baseline value (by ANCOVA).

A54. Where will the research take place? *(Tick as appropriate)*

- [x] UK
- [ ] Other states in European Union
- [ ] Other countries in European Economic Area
- [ ] Other

If Other, give details:

A55. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK, the European Union or the European Economic Area?

(•) Yes ( ) No

If Yes give details of each rejected application including:

Name of Research Ethics Committee or regulatory authority:	Nottingham Research Ethics Committe 2
Decision and date taken:	Application not approved.05.03.08
Research ethics committee reference number:	08/H0408/18

A56. In how many and what type of host organisations (NHS or other) in the UK is it intended the proposed study will take place?

Indicate the type of organisation by ticking the box and give approximate numbers if known:

	Number of organisations
☑ Acute teaching NHS Trusts	1
☐ Acute NHS Trusts	
☐ NHS Primary Care Trusts or Local Health Boards in Wales	
☐ NHS Trusts providing mental healthcare	
☐ NHS Health Boards in Scotland	
☐ HPSS Trusts in Northern Ireland	
☐ GP Practices	
☐ NHS Care Trusts	
☐ Social care organisations	
☐ Prisons	
☐ Independent hospitals	
☐ Educational establishments	
☐ Independent research units	
☐ Other (give details)	

Other:

A57. What arrangements are in place for monitoring and auditing the conduct of the research?

A data monitoring commitee (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.

A57a. Will a data monitoring committee be convened?

◉ Yes ○ No

If Yes, details of membership of the data monitoring committee (DMC), its standard operating procedures and summaries of reports of interim analyses to the DMC must be forwarded to the NHS Research Ethics Committee which gives a favourable opinion of the study.

What are the criteria for electively stopping the trial or other research prematurely?

The trial will be stopped prematurely if unblinded analysis by the DMC shows harm or overwhelming benefit from treatment. However in a sample size of 80 it is unlikely such difference will be demonstrated.

A58. Has external funding for the research been secured?

○ Yes ◉ No

If No, what arrangements are being made to cover any costs of the research? If no external funding is being sought, please say so:

Given the appropriate regulatory approval we would plan to commence this trial as soon as possible using resources already available with the Division of Stroke Medicine at the University of Nottingham. The unit is currently running several single centre trials, one international academic trial and participates in numerous commercial and academic trials. We have 13 full time member of staff and 2 part time members of staff as well as support form the national Stroke Research Network. However, we are seeking additional funding for this trial from charitable and research organisations.

A59. Has the funder of the research agreed to act as sponsor as set out in the Research Governance Framework?

○ Yes ◉ No

Has the employer of the Chief Investigator agreed to act as sponsor of the research?

◉ Yes ○ No

Lead sponsor *(must be completed in all cases)*

Name of organisation which will act as the lead sponsor for the research:

University of Nottingham

Status:

○ NHS or HPSS care organisation ◉ Academic ○ Pharmaceutical industry ○ Medical device industry ○ Other

If Other, please specify:

Address:	The University of Nottingham University Boulevard Nottingham
Post Code:	NG7 2RD
Telephone:	0115 9515151
Fax:	0115 9513666
Mobile:	
E−mail:	

Sponsor's UK contact point for correspondence with the main REC *(must be completed in all cases)*

Title: Mr Forename/Initials: Paul Surname: Cartledge

Work Address:	Research Innovations Department, University of Nottingham Kings Meadow Campus, Lenton Lane
Post Code:	NG7 2NR
Telephone:	0115 9515679
Fax:	
Mobile:	
E−mail:	paul.cartledge@nottingham.ac.uk

Co−sponsors

Are there any co−sponsors for this research?

○ Yes ◉ No

Legal representative* of the sponsor in the EU for the purpose of this trial *(if applicable)*

Title: Forename/Initials: Surname:

Work Address:

Post Code:
Telephone:
Fax:
Mobile:
E−mail:

** A legal representative must be appointed for a clinical trial of an investigational medicinal product if the sponsor is not established within the European Economic Area (EEA) (see article 19 of Directive 2001/20/EC). If this applies, enclose evidence that the legal representative is established within the EEA and has accepted the role of legal representative.*

A60. Has any responsibility for the research been delegated to a subcontractor?

○ Yes ◉ No

A61. Will individual *researchers* receive any personal payment over and above normal salary for undertaking this research?

○ Yes ◉ No

A62. Will individual *researchers* receive any other benefits or incentives for taking part in this research?

○ Yes ◉ No

A63. Will the host organisation or the researcher's department(s) or institution(s) receive any payment or benefits in excess of the costs of undertaking the research?

○ Yes ◉ No

A64. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share−holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

A65. Research reference numbers: *(give any relevant references for your study):*

Applicant's/organisation's own reference number, e.g. R&D (if available):	08SR003
Sponsor's/protocol number:	1.1
Funder's reference number:	
International Standard Randomised Controlled Trial Number (ISRCTN):	ISRCTN66434824
ClinicalTrials.gov Identifier (NCT number):	
European Clinical Trials Database (EudraCT) number:	2007−004766−40
Project website:	

A66. Other key investigators/collaborators *(all grant co−applicants or protocol co−authors should be listed)*

Title: Prof Forename/Initials: Jeffery Surname: Saver

Post:	Professor of Neurology, University of California
Qualifications:	BSc MD
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Postcode:	CA 90095
Telephone:	
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Title: Prof Forename/Initials: Gary Surname: Ford

Post:	Professor of Pharmacology of Old Age, University of Newcastle
Qualifications:	BA MB BChir MA FRCP
Organisation:	University of Newcastle
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Postcode:	NE1 4LP
Telephone:	0191 222 7744
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Title: Mr Forename/Initials: Carl Surname: Keeble

Post:	Divisional Clinical Manager, East Midlands Ambulance Service
Qualifications:	SRParamedic
Organisation:	East Midlands Ambulance Service
Work Address:	
Postcode:	
Telephone:	
Fax:	
Mobile:	

E−mail: Carl.Keeble@emas.nhs.uk

Title: Dr Forename/Initials: John Surname: Stephenson

Post: Clinical Director, East Midlands Ambulance Service
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Organisation: East Midlands Ambulance Service
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Title: Dr Forename/Initials: Gillian Surname: Sare

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Postcode: NG5 1PB
Telephone: 0115 8231770
Fax:
Mobile:
E−mail:

A67. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

This is an acute trial and treatment will only last a maximum of 7 days. Therefore no patient will need to continue study medication after the trial period is complete.

PART A: Summary of Ethical Issues

A68. Overview of the research

To provide all the information required by the REC, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A68−1. Lay summary. *Please provide a brief summary of the research (maximum 300 words) in lay language. This summary will be published on the website of the National Research Ethics Service following the ethical review.*

Stroke is a devastating disease affecting about 120,000 people in the UK alone each year. While it is important to try and prevent strokes from occurring, it becoming clear that if action is taken early after the onset of a stroke death and disability can be prevented. There are already new drugs available for stroke that can reduce death and disability if given within 3 hours of onset of symptoms and there are more drugs currently being developed which may also help.

These new treatment work on the premise that in the first few hours after the onset of a stroke, some brain tissue is still alive and salvagable but in danger of permanent damage. Developing new treatments that can save brain and therefore prevent death and disability are key areas of research. However, it can be difficult to test these treatments in stroke patients to see if they work as there are only a few hours available after the onset of symptoms when they can be administered. By the time a patient reaches hospital, the usual site for recruitment and treatment in acute stroke trials, these hours are often past. Involving the ambulance service in the identification of suitable patients, the process of randomising patients to treatments and the administration of these treatments may allow treatments for acute stroke to be tested more successfully.

In this study we aim to test whether the ambulance service is able to correctly identify acute stroke patients, randomise them to a treatment (in this case a blood pressure treatment) and administer the first dose of the treatment within 4 hours of onset of symptoms.

A68−2. Summary of main issues. *Please summarise the main ethical and design issues arising from the study and say how you have addressed them.*

There are several key ethical issues in this trial. Firstly, this would be the first trial in the UK using the ambulance service to identify and consent patients with suspected stroke into a clinical trial. This raises questions of the legitimacy of the paramedic in participating in clinical trials in stroke as an investigator. We believe that involving trained paramedics in clinical trials in acute stroke will be of benefit to patients and to the ambulance service. It is extremely difficult to recruit patients with stroke into clinical trials in the UK within the first few hours following stroke using the standard hospital based approach. As such it has been difficult to assess the benefits of acute treatments in the time they are most likely to be of benefit. Involving the ambulance service in

the identification and recruitment of patients will help to solve this. We believe that the design of this trial is such that using validated techniques such as the FAST assessment to identify stroke patients will mean that paramedics should be able to identify patients correctly. Also, it is now becoming more common for nurse consent in clinical trials and with the correct trianing, paramedic consent is an extension of this.

This trial also involved patients who are unable to consent. Stroke trials often involve incapacitated adults as the nature of stroke means that often patients have commincation difficulties. Without allowing for other methods of consent the stroke patients recruited to the trial would be mild strokes and those patients most likely to benefit from treatment would be excluded from the trial. Also, any results of the trial would not be applicable to a larger stroke population.

We propose that in the absence of available relatives in a patient who is unable to consent for themselves, the paramedic be able to enter the patient into the initial stage of the trial in the ambulance. This would involve only the application one GTN patch and taking a non−invasive blood pressure. No other research activity would take place until written consent from a relative is obtained in the hospital. We feel this approach would enable the recruitment of a wide range of stroke patients and the outcome of this trial may have wide implications for the ability to study neuroprotective agents in stroke patients.

We also propose using a real test treatment in this trial, rather than conduct a 'sham' trial. We feel this is essential to the validity of the results. We also feel that GTN is an ideal choice of test IMP for the reasons laid out in A9.

Question(s) 69−71 disabled.

PART B: Section 1 – List of proposed research sites

List below all research sites you plan to include in this study. The name of the site is normally the name of the acute NHS Trust, GP practice or other organisation responsible for the care of research participants. In some cases it may be an individual unit, private practice or a consortium – see the guidance notes.

Principal Investigators at other sites should apply to the relevant local Research Ethics Committee for site–specific assessment (SSA) using the Site–Specific Information Form. Applications for SSA may be made in parallel with the main application for ethical review (once the main REC has validated the application), or following issue of a favourable ethical opinion. Approval for each site will be issued to you by the main REC following SSA.

1. Name of the research site:

Nottingham University Hospitals NHS Trust

Principal Investigator for the study at this site:

Title: Prof Forename/Initials: Philip Surname: Bath

Post: Consultant Stroke Physician
Work Address: Clinical Sciences Building
City Hospital
Nottingahm
Postcode: NG5 1PB

PART B: Section 5 – Use of newly obtained human biological materials

1. What types of human tissue or other biological material will be included in the study?

Venous blood samples

2. Who will collect the samples?

The study doctor or nurse

3. Will the samples be: *(Tick as appropriate)*

☑ Obtained primarily for research purposes?
☐ Surplus (i.e. left over from tissue taken in the course of normal clinical care for diagnostic or therapeutic purposes)?

4. Will informed consent be obtained from donors for use of the samples:

In this research?

◉ Yes ○ No

In future research?

◉ Yes ○ No

5. Will the samples be stored:

In fully anonymised form? *(link to donor broken)*

○ Yes ◉ No

In linked anonymised form? *(linked to donor but donor not identifiable to researchers)*

◉ Yes ○ No

If Yes, say who will have access to the code and personal information about the donor.

Sample will be stored identifired with study name, study number initials and date of birth. This is to ensure correct identification of samples. Blood results once analysed will be compared with clinical data held on an anonymed trial database with only patient initials and trial number stored.

The only way of identifying the donor would be through finding patients' trial files where patient identifiable information would be kept. The blood results are not of clinical value and it is not expected that researchers would need to link then to patient themselves.

In a form in which the donor could be identifiable to researchers?

○ Yes ◉ No

If Yes, please justify:

6. What types of test or analysis will be carried out on the samples?

Surrogate markers of stroke, specifically S100, MMP and BNP. These blood test may allow us to see if patients receiving GTN have favourable surrogate outcome.

7. Will the research involve the analysis of human DNA in the samples?

○ Yes ◉ No

8. Is it possible that the research could produce findings of clinical significance for individuals? *(May include relatives as well as donors)*

○ Yes ◉ No

9. If so, will arrangements be made to notify the individuals concerned?

○ Yes ○ No ◉ Not applicable

If No, please justify. If Yes, say what arrangements will be made and give details of the support or counselling service.

10. Give details of where the samples will be stored, who will have access and the custodial arrangements.

Frozen blood samples will be stored. The chief investigator Prof Bath and his research team will have access to samples for analysis.

11. What will happen to the samples at the end of the research?

◉ Destruction

○ Transfer to research tissue bank
(If the bank is in England, Wales or Northern Ireland a licence from the Human Tissue Authority will be required to store the tissue for possible further research.)

○ Storage by research team pending ethical approval for use in another project
(Unless the researcher holds a licence from the Human Tissue Authority, a further application for ethical review should be submitted before the end of this project.)

○ Storage by research team as part of a new research tissue bank
(The bank will require a licence from the Human Tissue Authority. A separate application for ethical review of the tissue bank may also be submitted.)

○ Not yet known

Please give further details of the proposed arrangements:

PART B: Section 7 – Adults unable to consent for themselves

A. Clinical trials of investigational medicinal products – adults unable to consent for themselves

A1. What impairing condition(s) will the participants have?

Patients will have suffered from stroke which can prevent consent due to language difficulties and confusion.

A2. Could the trial be carried out equally effectively if confined to adults capable of giving consent?

○ Yes ◉ No

A3. How will the capacity of potential participants to consent to the research be assessed? Who in the research team will make the assessment and what knowledge of the participant or relevant training/experience will they have to enable them to undertake it?

Consent for the first part of the trial will be taken by paramedics who will be trained in consent for clinical trials and GCP. The paramedics are all experienced at taking consent in the ambulance in emergency situations for other treatments. They will read the patient a brief outline of the trial (as enclosed) and take verbal consent to participate. The patient will be asked if they understand what has been read to them, but in the ambulance the response to enter the first part of the trial will be immediate.

Full consent will be taken for continued participation in the trial during the first 24 hours in hospital. It will be taken by an experience trial nurse or doctor. The patient must be able to understand the trial and the implications of taking part, usually tested by asking the patient to explain the outline of the trial to the consenting investigator.

A4. What benefit is the administration of the investigational medicinal product expected to produce for these participants? *You may refer back to your answer to Question A18.*

The trial will not benefit patients directly but will assist in gaining knowledge about the best way to treat patients with acute stroke.

A5. Will the trial involve any foreseeable risk or burden for these participants, or interfere in any way with their freedom of action or privacy?

◉ Yes ○ No

If Yes, please give an assessment below. You may refer back to your answer to Questions A16 and A17. Highlight any risk, burden or discomfort specific to these participants. Justify in relation to the potential benefits.

There are scientific arguments which say that lowering blood pressure in acute stroke could be harmful, although there are also strong arguments it will be beneficial. The ENOS trial of GTN in acute stroke has treated > 700 patients to date and has not shown arm when the data is reviewed by the data monitoring committee and we conclude that the risk is small.

Stroke patients often cannot consent because of speech difficulties and it is impossible to carry out a trial of representative stroke patients without assent. If emergency trials in stroke only include patients who can give consent they would include only mild strokes and therefore exclude those patients most likely to benefit from intervention. The results would then not be generalisable to the population of stroke patients.

In addition, this trial aims primarily to assess whether ambulance led clinical trials in acute stroke are possible and part of this assessment is whether the paramedics are able to take consent and assent effectively. GTN may cause mild headache and the patch may cause a mild rash. Blood tests may cause mild discomfort and bruising. There are no additional scans in this trial.

A6. What arrangements will be made to identify and seek informed consent from a legal representative?

We propose that a patients relative give assent where they are available and this is possible. Paramedics will then approach the relative about participation in the trial in the ambulance. They will read a brief description of the trial to the relative and gain consent assent to administer trial medication in the ambulance. When the patient arrives in hospital they will be given a full relative information sheet and asked to assent to continued participation in the trial.

If the patient is unable to consent then we propose that the paramedics be able to enroll patients in the first stage of the trial and administer trial medication in the ambulance. Assent to continue in the trial will be gained once the patient is in hospital.

A7. Is it possible that a participant might need to be treated urgently as part of the trial before it is possible to identify and seek consent from a legal representative?

(•) Yes ( ) No

If Yes, outline how decisions will be made on the inclusion of participants and what arrangements will be made to seek consent from a legal representative as soon as practicable thereafter.

Stroke patients often lack the ability to consent. This is a hyperacute trial with patients randomised within 4 hours of stroke onset. If there is no relative available to act in place of the patient, then the paramedic crew may randomise suitable patients into the first stage of the trial. This will involve applying a gauze dressing +/– GTN patch the taking of non invasive blood pressures only. A patient will only continue in the trial if they become able to consent for themselves or a relative is available to give assent within the first 24 hours of entering the trial, i.e before any other research activity has taken place. All usual stroke interventions are allowed in this trial and so all treatments will receive best usual care in addition to trial procedures.

A8. What steps will you take to provide information about the trial to participants, according to their capacity of understanding, and to consider the explicit wishes of participants capable of forming an opinion?

All patients/relatives will have read the information sheets which should be understandable to all. An investigator will be able to answer all questions at all levels about the trial over and above the information provided in the information sheets. The explicit wishes of all patients able to form an opinion will be honored.

A9. What will be the criteria for withdrawal of participants?

A patient may withdraw from the trial at any stage through choice. Unless a patient (or relative) withdraws from the trial all patients will remain enrolled in the trial until follow up at 90 days is complete. During the 7 day treatment period of the trial, the treatment (but now follow up) may be withdrawn if the patient experiences unacceptable side effects or hypotension.

PART B: Section 8 – Declarations

Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.
3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application of which the main REC has given a favourable opinion and any conditions set out by the main REC in giving its favourable opinion.
4. I undertake to seek an ethical opinion from the main REC before implementing substantial amendments to the protocol or to the terms of the full application of which the main REC has given a favourable opinion.
5. I undertake to submit annual progress reports setting out the progress of the research.
6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer.
7. I understand that research records/data may be subject to inspection for audit purposes if required in future.
8. I understand that personal data about me as a researcher in this application will be held by the relevant RECs and their operational managers and that this will be managed according to the principles established in the Data Protection Act.
9. I understand that the information contained in this application, any supporting documentation and all correspondence with NHS Research Ethics Committees or their operational managers relating to the application:

   – Will be held by the main REC until at least 3 years after the end of the study.

   – May be disclosed to the operational managers or the appointing body for the REC in order to check that the application has been processed correctly or to investigate any complaint.

   – May be seen by auditors appointed by the National Research Ethics Service to undertake accreditation of the REC.

   – Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.
11. I understand that the lay summary of this study will be published on the website of the National Research Ethics Service (NRES) as it appears in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

Signature: .....

Print Name:

Date: (dd/mm/yyyy)

Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the sponsor nominated to take the lead for the REC application.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.*
3. Any necessary indemnity or insurance arrangements, as described in question A35, will be in place before this research starts.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The duties of sponsors set out in the NHS Research Governance Framework for Health and Social Care will be undertaken in relation to this research.**
7. The statutory responsibilities of sponsors set out in the Medicines for Human Use (Clinical Trials) Regulations 2004 will be undertaken in relation to this trial.
8. I understand that the lay summary of this study will be published on the website of the National Research Ethics Service (NRES) as it appears in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

* Not applicable to student research (except doctoral research).
** Not applicable to research outside the scope of the Research Governance Framework.

Signature: .....

Print Name:

Post:

Organisation:

Date: (dd/mm/yyyy)

Site–Specific Information Form

Does this application relate to a research site for which the NHS (or HPSS in Northern Ireland) is responsible or to a non–NHS research site?

- (•) NHS site
- ( ) Non–NHS site

For HPSS sites in Northern Ireland, separate arrangements are in place for R&D applications. There is no need to complete questions marked "R&D only" on this form.

This question must be completed before proceeding. The filter will customise the form, disabling questions which are not relevant to this application.

In which country is the research site located?

- (•) England
- ( ) Wales
- ( ) Scotland
- ( ) Northern Ireland

The data in this box is populated from Part A:

Short title and version number:
RIGHT Trial

Name of NHS Research Ethics Committee to which application for ethical review is being made:
Nottingham 2

Project reference number from above REC: 09/H0408/5

Name of NHS REC responsible for SSA:
Nottingham 2

SSA reference (for REC office use only)

Name of NHS care organisation to which application is being made for permission to conduct the research:
Nottingham University Hospitals NHS Trust

NHS organisation reference (for R&D office use only):

1. Title of the research *(populated from A1)*

Full title: Determining the potential of ambulance–based randomised controlled trials in patients with hyperacute stroke; assessment of GTN in lowering blood pressure

Key words: stroke, ambulance, blood pressure

2. Name of Chief Investigator *(populated from A2)*

Title:	Forename/Initials:	Surname:
Prof	Philip	Bath

3. Name of organisation acting as lead sponsor for the study *(populated from A59)*

University of Nottingham

4. Research reference numbers if known *(populated from A65)*

Applicant's/organisation's own reference number, e.g. R&D:	08SR003
Sponsor's/protocol number:	1.1
Funder's reference number:	
International Standard Randomized Controlled Trial Number (ISRCTN):	ISRCTN66434824
ClinicalTrials.gov Identifier (NCT number):	
European Clinical Trials Database (EudraCT) Number:	2007−004766−40
Project website:	

6. Give the name of the NHS site within or through which the research will take place under the responsibility of the PI or Local Collaborator. *Please give the name only. Further details of locations should be given in question 8. The name of the site is normally the name of the relevant NHS organisation. Each NHS general or dental practice is a separate site unless a formal consortium/network is in place.*

Nottingham University Hospitals

Is this a primary care site?

○ Yes ◉ No

If Yes, give the name of the primary care organisation responsible for the site below:

7. Was this site listed as a planned trial site in the original applications to the main Research Ethics Committee and the MHRA?

◉ Yes ○ No

If No, the sponsor should also submit a Notice of Amendment form to the main REC, copied to the MHRA for information.

8. Specify all locations, departments, groups or units at which or through which research procedures will be conducted at this site and describe the activity that will take place.

List all locations/departments etc where research procedures will be conducted within the NHS organisation, describing the involvement in a few words. Where access to specific facilities will be required these should also be listed for each location.

Name the main location/department first. Include details of any centres at other NHS organisations where potential participants may be seen or referred for inclusion in the research at this site. Give details of any research procedures to be carried out off site, for example in participants' homes.

	Location	Activity/facilities
1	EMAS ambulance service ambulances	Limited consent, blood pressure monitoring, treatment application
2	A&E	Full consent, blood pressure monitoring, blood taking, assessment of patient.
3	Berman 1 stroke unit	Full consent, blood pressure monitoring, blood taking, assessment of patient.
4	Stroke rehab wards	Assessment of patient. Blood taking.

12. Who is the Principal Investigator or Local Collaborator for this research at this site?

Title:	Forename/Initials:	Surname:
Prof	Philip	Bath

Post: Consultant Stroke Physician

Qualifications: MBBS MD FRCP FRCPath

Organisation: Nottingham University Hospitals MHS Trust

Work Address: Division of Stroke Medicine
Clinical Sciences Building, City Hospital
Nottingham

Postcode: NG5 1PB

E–mail: philip.bath@nottingham.ac.uk

Telephone: 0115 8231768
Fax: 0115 8231765
Mobile:

	R&D Only
a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care?	(•) Yes ( ) No
b) Does this person hold a current substantive or honorary contract with the NHS organisation or accepted by the NHS organisation?	(•) Yes ( ) No

Please provide a copy of the c.v. for the PI.

If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D office.

14. Give details of all other members of the research team at this site, including academic supervisors and all people who will interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care.

1. Research Member

Title:	Forename/Initials:	Surname:
Mrs	Margaret	Adrian

Employing organisation: University of Nottingham

Post: Research Nurse

Qualifications: RN

Role in research team: researcher

R&D Only

a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care?	Yes / No
b) Does this person hold a current substantive or honorary contract with the NHS organisation or accepted by the NHS organisation?	Yes / No

Please provide a copy of the c.v. for the research team member.

If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D office.

2. Research Member

Title:	Forename/Initials:	Surname:
	Paramedics	

Employing organisation: East Midlands Ambulance Service

Post: Paramedic

Qualifications:

Role in research team: researcher

R&D Only

a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care?	Yes / No
b) Does this person hold a current substantive or honorary contract with the NHS organisation or accepted by the NHS organisation?	Yes / No

Please provide a copy of the c.v. for the research team member.

If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D office.

3. Research Member

Title:	Forename/Initials:	Surname:
Dr	Tim	England

Employing organisation: University of Nottingham

Post: Research Fellow

Qualifications: MBChB, MRCP

Role in research team: researcher

R&D Only

a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care?	Yes / No
b) Does this person hold a current substantive or honorary contract with the NHS organisation or accepted by the NHS organisation?	Yes / No

Please provide a copy of the c.v. for the research team member.

If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D

office.

4. Research Member

Title:	Forename/Initials:	Surname:
Dr	Gillian	Sare

Employing organisation: University of Nottingham

Post: Research Fellow

Qualifications: MBChB

Role in research team: researcher

R&D Only

a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care? (●) Yes ( ) No

b) Does this person hold a current substantive or honorary contract with the NHS organisation or accepted by the NHS organisation? (●) Yes ( ) No

Please provide a copy of the c.v. for the research team member.

If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D office.

5. Research Member

Title:	Forename/Initials:	Surname:
Mrs	Fiona	Hammonds

Employing organisation: University of Nottingham

Post: Research Nurse

Qualifications: RN

Role in research team: researcher

R&D Only

a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care? (●) Yes ( ) No

b) Does this person hold a current substantive or honorary contract with the NHS organisation or accepted by the NHS organisation? (●) Yes ( ) No

Please provide a copy of the c.v. for the research team member.

If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D office.

6. Research Member

Title:	Forename/Initials:	Surname:
Dr	Chamila	Geeganage

Employing organisation: University of Nottingham

Post: Research Fellow

Qualifications: MBBS, MSc

Role in research team: researcher

	R&D Only
a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care?	(•) Yes ( ) No
b) Does this person hold a current substantive or honorary contract with the NHS organisation or accepted by the NHS organisation?	(•) Yes ( ) No

Please provide a copy of the c.v. for the research team member.

If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D office.

7. Research Member

Title:	Forename/Initials:	Surname:
Dr	Wayne	Sunman

Employing organisation: Nottingham University Hospitals NHS Trust

Post: Consultant Physican

Qualifications: FRCP

Role in research team: researcher

	R&D Only
a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care?	(•) Yes ( ) No
b) Does this person hold a current substantive or honorary contract with the NHS organisation or accepted by the NHS organisation?	(•) Yes ( ) No

Please provide a copy of the c.v. for the research team member.

If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D office.

8. Research Member

Title:	Forename/Initials:	Surname:
Dr	Sandeep	Ankolekar

Employing organisation: University of Nottingham

Post: Research Fellow

Qualifications: MRCP

Role in research team: researcher

R&D Only

a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care? (●) Yes ( ) No

b) Does this person hold a current substantive or honorary contract with the NHS organisation or accepted by the NHS organisation? (●) Yes ( ) No

Please provide a copy of the c.v. for the research team member.

If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D office.

9. Research Member

Title:	Forename/Initials:	Surname:
Mrs	Lynn	Stokes

Employing organisation: University of Nottingham

Post: Research Metrologist

Qualifications: BA(hons), RM

Role in research team: researcher

R&D Only

a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care? (●) Yes ( ) No

b) Does this person hold a current substantive or honorary contract with the NHS organisation or accepted by the NHS organisation? (●) Yes ( ) No

Please provide a copy of the c.v. for the research team member.

If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D office.

15. Does the Principal Investigator or any other member of the site research team have any direct personal involvement (e.g. financial, share–holding, personal relationship etc) in the organisation sponsoring or funding the research that may give rise to a possible conflict of interest?

( ) Yes (●) No

If Yes, give further details:

16. What is the proposed local start and end date for the research at this site?

Start date:	01/02/2009 *(dd/mm/yyyy)*
Duration (Months):	24
End date:	31/01/2011 *(dd/mm/yyyy)*

17. Summary of the research *(populated from A10−1)*

Stroke is a devastating disease affecting about 120,000 people in the UK alone each year. While it is important to try and prevent strokes from occuring, it becoming clear that if action is taken early after the onset of a stroke death and disability can be prevented. There are already new drugs available for stroke that can reduce death and disability if given within 3 hours of onset of sypmtoms and there are more drugs currently being developed which may also help.

These new treatment work on the premise that in the first few hours after the onset of a stroke, some brain tissue is still alive and salvagable but in danger of permenant damage. Developing new treatments that can save brain and therefore prevent death and disability are key areas of research. However, it can be difficult to test these treatments in stroke patients to see if they work as there are only a few hours available after the onset of symptoms when they can be administered. By the time a patient reaches hospital, the usual site for recruitment and treatment in acute stroke trials, these hours are often past. Involving the ambulance service in the identification of suitable patients, the process of randomising patients to treatments and the administration of these treatments may allow treatments for acute stroke to be tested more successfully.

In this study we aim to test whether the ambulance service is able to correctly identify acute stroke patients, randomise them to a treatment (in this case a blood pressure treatment) and administer the first dose of the treatment within 4 hours of onset of symptoms.

In order to properly test whether the ambulance service can run a trial we need a drug to test and we propose using a blood pressure treatment. It is important to use a real treatment to test, as conducting a 'sham' trial would not truly test whether or not the paramedics can recruit and treat patients with real medication. High blood pressure is common in the first hours and days following a stroke and we know from studies that these patients are more likely not to recover fully and be left with some disability. At present, doctors do not routinely treat high blood pressure in these first hours and days after a stroke. Lowering blood pressure in this early stage after a stroke with medications might help patients to recover. This question is already being studied by a large international trial called the ENOS trial which recruit patients with high blood pressure up to 48 hours after the onset of stroke. However, in the ENOS trial few patients are included in the study within 4 hours of onset of their stroke because of the problems outlined above and therefore the treatment is not given at a time when it is most likely to be beneficial. In the RIGHT trial we want to use the same blood pressure lowering drug as the ENOS trial, Glyceryl Trinitrate or GTN (a along established much used drug to treat angina) to lower blood pressure. This drug has the advantage that is comes in a patch and can be given to all stroke patients even if the stroke has affected thier swallow. We also have considerable safety data on the use of GTN in acute stroke as we have randomised more than 1,000 patients into trials using GTN in acute stroke, and we know the side effect/complication rate to be very low.

The primary aim of this trial is to assess whether it is feasible to use the ambulance service to recruit stroke patients into clinical trials with 4 hours of the onset of their symptoms. Secondary information will be gained on the effects of GTN on blood pressure and other measures in patients with stroke.

Patients who have the symptoms of a stroke and who telephone for an ambulance will be assessed by the paramedics who come to their aid. The paramedics will confirm whether they are likely to have had a stroke by using an assessment designed for non−doctor heath care workers called the FAST test. This assesses whether a person has face or arm weakness or speech difficulty which are very common in stroke. The FAST test has been shown to be successful in identifying patients with stroke.

If the patients fits the criteria the paramedics will explain that if they wish they may enter the clinical trial. 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 blood pressures taken in the ambulance and for the first 24 hours in hospital. No further research activities would be carried out until further consent has been taken in the hospital. If the patient cannot consent for themselves (stroke aften 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.

The patient will then be randomised to receive either a GTN patch or no patch (the control). A preprapred envelope will be in each ambulance ready for use. Patients with no patch will have a gauze swab placed where the patch would

be in order to try and hide which treatment they are receiving from them. The patient would have blood pressures taken 2 hours after the patch goes on and 1 extra blood pressure measurement every day for 7 days, which is the length of time they would be treated with the GTN/control. The patch and/or gauze swab is changed every day. After 7 days there are no more treatments in this trial.

Patients will have 2 blood tests during the course of the trial. The first will be on the first day after full consent or assent has been taken in hospital and the second will be on day 4. These will be examined for surrogate markers of stroke to see if treated patients do better than those that aren't treated.

Patients would have their disability level assessed by a nurse 1 week after their stroke (or sooner if they leave hospital sooner) and they would also have a telephone call after 3 months to see how they are. This phone call will ask how they are functioning physically as also perform short tests of memory, mood and quality of life.

All other treatments for stroke are exactly as they would normally be, including giving asprin, cholesterol tablets and other blood pressure tablets if required. Patients will be able to have physio and occupational therapy as normal. The trial involves no additional scans.

18. Details of clinical interventions *(populated from A12 where enabled)*

Additional Intervention	Average number per participant		Average time taken	Details of additional intervention or procedure, who will undertake it, and what training they have received.
	Routine Care	Research		
Other	0	7	2 minutes	Application of 5mg transdermal GTN patch if randomised to do so, or of a gause patch only if randoised to control. The study nurse or doctor will apply the patch.
Other		9	3 minutes	A non invasive blood pressure will be taken by the study nurse or doctor with an OMRON BP machine. Twice on the first day and then daily for 7 days.
Venepuncture		2	5 minutes	The research nurse or doctor will take blood on day 1 and day 4 of the trial. They will be trained in venopuncture according to hospital policy.

19. Details of non–clinical interventions *(populated from A13 where enabled)*

Additional Intervention	Average number per participant	Anticipated average time taken	Details of additional intervention or procedure, who will undertake it, and what training they have received.
Face to Face Interview	1	30 mins	The interview will be carried out by a research nurse experienced in clinical trials and trained in GCP and the EU directive.

20. Will any aspects of the research at this site be conducted in a different way to that described in Parts A and B or the study protocol?

○ Yes ◉ No

If Yes, explain and give reasons.

21. How many research participants/samples is it expected will be recruited/obtained from this site?

80 (all)

22. Give details of how potential participants will be identified locally and who will be making the first approach to them to take part in the study?

Participants will be identified by paramedics involved in the patients usual medical care and will be initially approach and consented by them.

23. Who will be responsible for obtaining informed consent at this site? What expertise and training do these persons have in obtaining consent for research purposes?

1 ☐	Prof Philip Bath	
2 ☑	Mrs Margaret Adrian	GCP trained and experienced in clinical trials
3 ☑	Paramedics	Paramedics will be trained by the research team to take consent and assent for clincial trials and in filling out the relevant CRFs.
4 ☑	Dr Tim England	GCP trained and experienced in clinical trials
5 ☑	Dr Gillian Sare	GCP trained and experienced in clinical trials
6 ☑	Mrs Fiona Hammonds	GCP trained and experienced in clinical trials
7 ☑	Dr Chamila Geeganage	GCP trained and experienced in clinical trials
8 ☐	Dr Wayne Sunman	
9 ☑	Dr Sandeep Ankolekar	GCP trained and experienced in clinical trials
10 ☑	Mrs Lynn Stokes	GCP trained and experienced in clinical trials

24. What local arrangements will be made to seek consent from a legal representative on behalf of adults unable to consent for themselves?

In the ambulance paramedics will be able to take take relative assent. They will also be able to enroll patients unable to consent without relatives present by enrolling them in a limited section of the trial.
In hospital full relative assent will be taken for all patients unable to consent.

27. Is there a contact point where potential participants can seek independent advice about participating in the study?

This is an acute trial and it is unlikely that patients will be able to seek external advice before joining the trial. Once enrolled, the PALS service and independent doctors in the hospital can provide advice as needed.

R&D Only

28. Please provide a copy on headed paper of the participant information sheet and consent form that will be used locally. *This must be the same generic version submitted to/approved by the main REC for the study while including relevant local information about the site, investigator and contact points for participants (see guidance notes).*

If you consider that changes should be made to the generic content of the information sheet to reflect site–specific issues in the conduct of the study (see 20), give details below. A substantial amendment may need to be discussed with the Chief Investigator and submitted to the main REC.

29. What arrangements have been made for participants who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? *(e.g. translation, use of interpreters etc.) (Populated from A29)*

In this emergency trial it is not practical to be able to provide paramedics who are able to speak other languages and as such we will not seek to recruit patients who cannot understand English sufficient to understand the trial.
What local arrangements have been made to meet these requirements (where applicable)?Not applicable

30. What arrangements will be made to inform the GP or other health care professionals responsible for the care of the participants?

A GP letter will be sent to each participants GP informing them of their involvement in the trial

33. What arrangements (e.g. facilities, staffing, psychosocial support, emergency procedures) will be in place at the site, where appropriate, to minimise the risks to participants and staff and deal with the consequences of any harm?

There are no specific arrangements.

R&D Only

37. Will any external funding be provided for the research at this site?

(•) Yes ( ) No

If Yes, indicate the source and details of the funding:

1. Source: University of Nottingham, Division of Stroke Medicine.

Type of funding	Details (including breakdown over years if appropriate)
(i) Block grant	
(ii) Per participant	
(iii) Other (give details)	The University will bear the cost of paying for investigational staff to conduct the trial.

R&D Only

38. Which organisation will receive and manage this funding?

University of Nottingham, Division of Stroke Medicine.

R&D Only

39. Authorisations required prior to R&D approval

This section deals with authorisations by managers within the NHS organisation. It should be signed in accordance with the guidance provided by the NHS organisation. This may include authorisation by line managers, service managers, support department managers, pharmacy, data protection officers or finance managers, depending on the nature of the research. Managers completing this section should confirm in the text what the authorisation means, in accordance with the guidance provided by the NHS organisation. This section may also be used by university employers or research staff to provide authorisation to NHS organisations, in accordance with guidance from the university.

1. Type of authorisation:

From Clinical Stroke Lead at NUH

Signature: .....

Date: .....

Title:	Forename/Initials:	Surname:
Mrs	Dawn	Goode

Organisation: Nottingham University Hospitals NHS Trust

Post: Clinical Stroke Lead

Work Address: City Hospital

Nottingham

Telephone:

Fax:

Postcode: NG5 1PB

Mobile:

E–mail: Dawn.Good@nuh.nhs.uk

Declarations

Declaration by Principal Investigator or Local Collaborator

1. The information in this form is accurate to the best of my knowledge and I take full responsibility for it.
2. I undertake to abide by the ethical principles underpinning the World Medical Association's Declaration of Helsinki and relevant good practice guidelines in the conduct of research.
3. If the research is approved by the main REC and NHS organisation, I undertake to adhere to the study protocol, the terms of the application of which the main REC has given a favourable opinion and the conditions requested by the NHS organisation, and to inform the NHS organisation within local timelines of any subsequent amendments to the protocol.
4. If the research is approved, I undertake to abide by the principles of the Research Governance Framework for Health and Social Care.
5. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to the conduct of research.
6. I undertake to disclose any conflicts of interest that may arise during the course of this research, and take responsibility for ensuring that all staff involved in the research are aware of their responsibilities to disclose conflicts of interest.
7. I understand and agree that study files, documents, research records and data may be subject to inspection by the NHS organisation, the sponsor or an independent body for monitoring, audit and inspection purposes.
8. I take responsibility for ensuring that staff involved in the research at this site hold appropriate contracts for the duration of the research, are familiar with the Research Governance Framework, the NHS organisation's Data Protection Policy and all other relevant policies and guidelines, and are appropriately trained and experienced.
9. I undertake to complete any interim and/or final reports as requested by the NHS organisation and understand that continuation of permission to conduct research within the NHS organisation is dependent on satisfactory completion of such reports.
10. I undertake to maintain a project file for this research in accordance with the NHS organisation's policy.
11. I take responsibility for ensuring that all serious adverse events are handled within the NHS organisation's policy for reporting and handling of adverse events.
12. I understand that information relating to this research, and about me as a researcher, will be held by the R&D office and may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.
13. I understand that information relating to this research, and about me as a researcher, will be held by RECs undertaking site−specific assessment and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.
14. I understand that the information contained in this application, any supporting documentation and all correspondence with the R&D office and/or the REC system relating to the application will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
15. I understand that information relating to this research (including my contact details) may be publicly available through the National Research Register.

Signature of Principal Investigator or Local Collaborator: .....

Print Name:

Date: 06/01/2009