

NIHR HTA Programme

22 November 2012

The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

Health Technology Assessment Programme
National Institute for Health Research
Evaluation, Trials and Studies Coordinating Centre
University of Southampton, Alpha House
Enterprise Road, Southampton, SO16 7NS

tel: +44(0)23 8059 5586

email: hta@hta.ac.uk

fax: +44(0)23 8059 5639

web: www.hta.ac.uk

Stroke Oxygen Study



A multi-centre, prospective, randomised, open, blinded-endpoint study to assess whether routine oxygen treatment in the first 72 hours after a stroke improves long-term outcome

Version 2 17.04.2008
Amendment 6 03.10.2012

Chief Investigator
Dr C. Roffe

Trial Management Committee
Prof Peter Crome
Prof R Gray
Prof P Jones
Dr C. Roffe
Dr S. Pountain
StrokesRUs (Linda and Peter Handy)

TABLE OF CONTENTS

1. Trial Summary	3
2. Trial Flow chart	4
3. General information and Contacts	5
4. Background	5
Why is there a need to investigate the effects of oxygen supplementation after stroke?	6
What is the justification for the fixed dose oxygen regime suggested for this study?....	7
What are the advantages of giving routine oxygen supplementation at night only?	7
5. Study aim and hypothesis	8
6. Study protocol	8
Study design	8
Recruitment	8
Inclusion criteria.....	8
Exclusion criteria	9
Intervention	9
Blinding	10
Initial assessment (see randomisation form)	10
Follow-up Assessments	10
7. Outcome measures	11
8. Data management and evaluation	12
Randomisation	12
Data management	12
Study size	13
9. Ethical Requirements	13
Approval of the study by the Research Ethics Committee	13
Good Clinical Practice	13
Patient Information and Consent	13
Monitoring of suspected unexpected serious adverse reactions (SUSARs)	14
Data protection	15
10. Trial Administration	15
Sponsor	15
Person authorized by the sponsor to act on behalf of the sponsor	15
Chief Investigator (CI)	15
Trial Management Committee (TMC)	15
Trial Steering Committee (TSC)	15
Data and Safety Monitoring Committee (DMSC)	15
International Advisory Committee (IAC)	16
11. References	17

1. Trial Summary

Mild hypoxia is common in stroke patients and may have significant adverse effects on the ischaemic brain after stroke. The use of oxygen treatment is rapidly increasing in European stroke units. A questionnaire survey of UK stroke physicians showed that almost 50% of respondents would start oxygen supplementation after stroke at a level of oxygen saturation of 95% or above, which is well within the normal physiological range. Oxygen treatment is not without side effects. It impedes early mobilisation, could pose an infection risk, and may encourage the formation of toxic free radicals leading to further damage to the ischaemic brain. A study of routine oxygen supplementation given for 24 h at a rate of 3L/min published in 1999 (Ronning and Guldvog) has shown no benefit in unselected patients, and potential harm in patients with mild strokes. In the Stroke Oxygen Pilot Study^{64 65} the flow rate of oxygen was lower (2 or 3 L/min dependent on baseline oxygen saturation) and treatment was continued for longer (72 hours). Neurological recovery at one week was better in the oxygen group and after correction for difference in baseline stroke severity and prognostic factors there was a trend to better outcome with oxygen at 6 months. In contrast to the earlier study by Ronning and Guldvog oxygen was as effective in mild as in severe strokes. These results are promising, but need confirmation in a larger study.

Oxygen saturation is lower at night than during the day, and episodes of oxygen desaturation are common during sleep. Nocturnal oxygen supplementation is likely to reduce the burden of hypoxia without interfering with daytime mobilisation and rehabilitation.

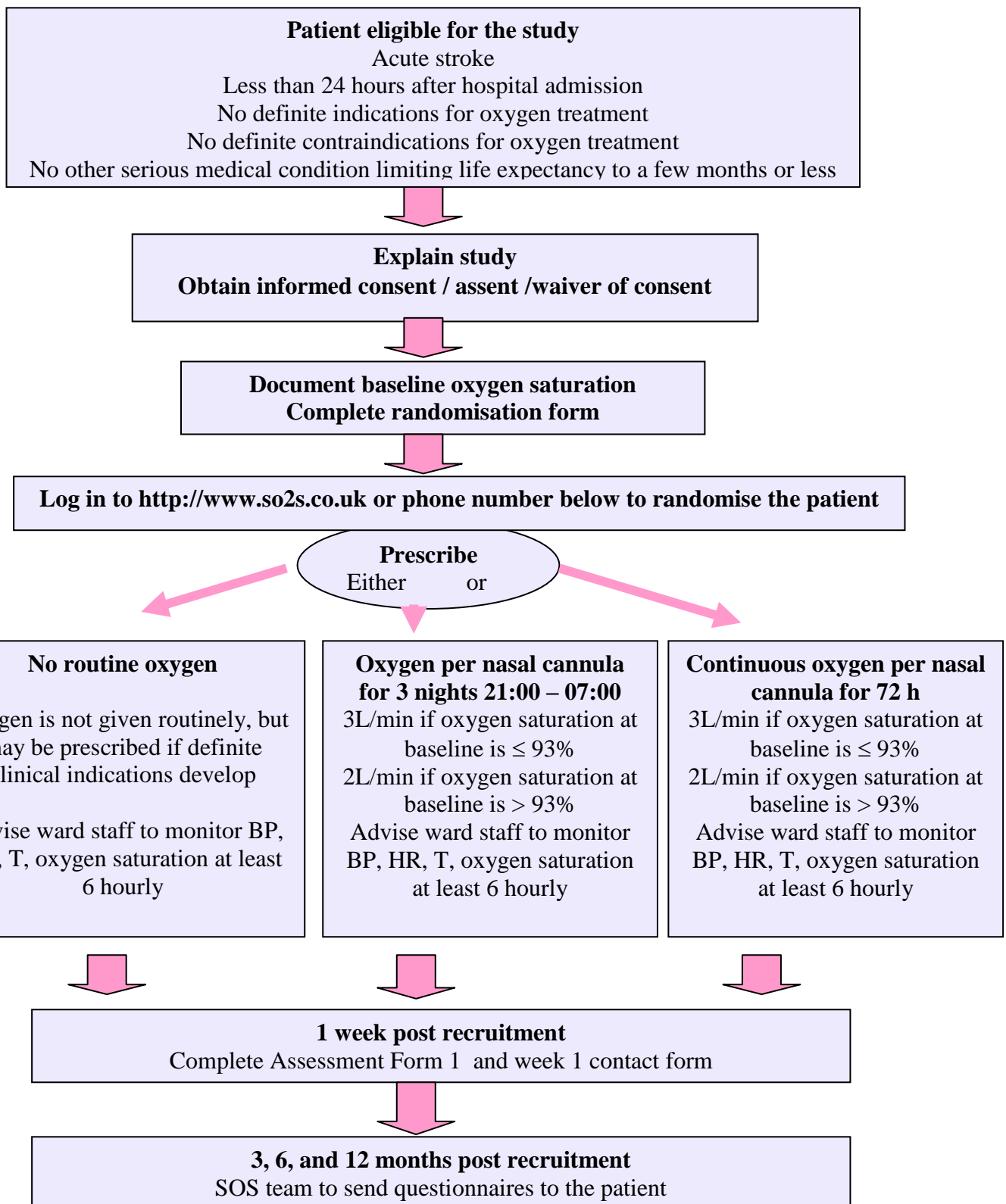
Before wider use of oxygen supplementation becomes established it is important to obtain better evidence on which patients benefit from such treatment. **SOS** is a large 'real life' trial which aims to produce reliable evidence on the balance of benefits and risks for different patient groups by randomising a large number of patients to routine oxygen supplementation or no routine oxygen treatment. The information on a few thousand patients randomised in **SOS** will help to guide the treatment of many thousands of future patients.

To make recruitment of a large, heterogeneous group of patients practicable procedures are kept simple, and eligibility is based on 'uncertainty'. Patients admitted to hospital with an acute stroke for whom there is substantial uncertainty whether or not they should receive oxygen or not are randomised to continuous oxygen treatment, nocturnal oxygen treatment or standard therapy (no routine oxygen) for 72 hours. Oxygen will be given at a rate of 2 or 3 litres/minute depending on baseline oxygen saturation. In this trial the extra work for collaborators is absolutely minimal. In addition to the randomisation form there is a one page baseline assessment and a brief clinical review at one week. Outcome data at 3, 6 and 12 months will be by a questionnaire sent to the patient by the trial centre. The success of **SOS** depends on the wholehearted support of doctors involved in acute stroke management. For this reason, publication of the final results will be in the names of all the collaborators, and not those of the principal investigators.

2. Trial Flow chart



Stroke Oxygen Study



Please contact Dr C. Roffe, Stroke Research Office, North Staffs. Combined Healthcare NHSTrust, Holly Lodge, 62 Queens Road, Hartshill, Stoke-on-Trent, ST4 7LH for randomisation, adverse events, or any queries daytime 0300 123 0891, nights and weekends 07740372852 (main) or 07734 068408 (back up)

3. General information and Contacts

TRIAL MANAGEMENT COMMITTEE

Dr Christine Roffe
Prof. Peter Jones
Prof. Peter Crome
Prof. Richard Gray
Dr Sarah Pountain
StrokesRUs (Mr Peter and Mrs Linda Handy)

TRIAL STEERING COMMITTEE

Prof. Richard Lindley
Prof. Martin Dennis
Prof. Lalit Kalra
Prof Sian Maslin-Prothero
Jane Daniels
Mrs Peta Bell

PATIENT REPRESENTATIVES

Peter and Linda Handy
Mrs Peta Bell

INTERNATIONAL ADVISORY COMMITTEE

Prof. Richard Lindley

DATA MONITORING AND SAFETY COMMITTEE

Prof. Stephen Jackson
Prof. Thompson Robinson
Dr Martyn Lewis

OFFICE

For general queries, supply of trial materials and collection of data: Stroke Research Office,
North Staffs. Combined Healthcare NHS Trust, Holly Lodge, 62 Queens Road, Hartshill,
Stoke-on-Trent ST4 7LH
Tel 0300 123 0891 Fax 0300 123 0894

24 HOUR RANDOMISATION

<http://www.so2s.co.uk>

EMERGENCY CONTACT DETAILS

Dr C. Roffe, Stroke Research Office, North Staffs. Combined Healthcare NHS Trust, Holly
Lodge, 62 Queens Road, Hartshill, Stoke-on-Trent ST4 7LH
mobile no 07740 372852 (main), 07734 068408 (back-up),

SPONSOR DETAILS

North Staffordshire Combined Healthcare Trust, Research and Development Department,
Directorate of Medicine and Clinical Effectiveness, Harplands Hospital, Hilton Road, Stoke-
on-Trent, ST4 6TH
Tel: 01782 441651, Fax: 01782 441624

FUNDING

Research for Patient Benefit, National Institute for Health Research

RESEARCH ETHICS COMMITTEE

North Staffs. Research Ethics Committee, North Staffs Medical Institute, Hartshill Road,
Stoke-on-Trent ST4 7NY
Fax 01782 714975

4. Background

Why is there a need to investigate the effects of oxygen supplementation after stroke?

It is now well established that specialist care on stroke units is effective in preventing death and disability after stroke (1). It does, however, still remain unclear which aspects of stroke care are crucial for improving outcome. It has been shown that patients on a stroke unit are more likely to receive oxygen than on a non specialised general ward (2). Mild hypoxia is common in stroke patients and may have significant adverse effects on the ischaemic brain after stroke (3). Hypoxaemia in the first few hours after hospital admission is associated with an increased risk of death (4). While healthy adults with normal cerebral circulation can compensate for mild hypoxia by an increase in cerebral blood flow (5), this is not possible in the already ischaemic brain after stroke (6-8). The use of oxygen treatment is rapidly increasing in European stroke units. A questionnaire survey of UK stroke physicians showed that almost 50% of respondents would start oxygen supplementation after stroke at an oxygen saturation of 95% or above (9), which is well within the normal physiological range (10). In many Accident and Emergency departments oxygen is given routinely to stroke patients irrespective of blood oxygen levels.

Oxygen treatment is not without side effects (11). It impedes early mobilisation and could pose an infection risk. There is evidence from animal models and in vitro studies that oxygen encourages the formation of toxic free radicals leading to further damage to the ischaemic brain (12-15), especially during reperfusion. Marked changes in ATP and related energy metabolites develop quickly in response to acute ischaemia and tissue hypoxia. These alterations are only partially reversed on reperfusion despite improved oxygen delivery. Ischemia-induced decreases in the mitochondrial capacity for respiration result in reduced oxygen consumption and further increase free radical generation during reperfusion (16). Oxidative stress has also been implicated in the activation of cell signalling pathways which lead to apoptosis and neuronal cell death (17, 18) While much research points towards adverse effects of hyperoxia in the ischaemic brain there is also evidence to support the notion that therapy-induced eubarc hyperoxia may be neuroprotective (19,20). Routine oxygen supplementation for acute myocardial infarction has been abandoned after a clinical trials showed no benefit, and potential harm (21). A quasi randomised study of oxygen supplementation for acute stroke by Ronning and Guldvog has shown that routine oxygen treatment in unselected stroke patients does not reduce morbidity and mortality. Subgroup analyses suggested that patients with severe strokes were more likely to benefit than those with mild strokes, but the study size was too small to define patients who are likely to derive benefit with certainty (22). A recent very small study of high flow oxygen treatment after acute stroke showed that cerebral blood volume and blood flow within ischaemic regions improved with hyperoxia. By 24 hours magnetic resonance imaging of the brain showed reperfusion in 50% of hyperoxia-treated patients versus 17% of controls ($p=0.06$) but no long term clinical benefit at 3 months (23). In the recently completed Stroke Oxygen Pilot Study^{64 65} the flow rate of oxygen was lower (2 or 3 L/min dependent on baseline oxygen saturation) and treatment was continued for longer (72 hours). Neurological recovery at one week was better in the oxygen group than in controls. While there was no difference in outcome at 6 months on direct comparison, there was a trend for better outcome with oxygen after correction for differences in baseline stroke severity and prognostic factors. In contrast to the earlier study by Ronning and Guldvog oxygen was as effective in mild as in severe strokes. These results are promising, but need confirmation in a larger study.

Clinical guidelines on oxygen supplementation after stroke are not based on evidence from randomized clinical trials, differ from country to country and change over time without obvious reason. The European Stroke Initiative (2008) suggests that routine oxygen

supplementation to all stroke patients has not been shown to be effective, but that adequate oxygenation is important, and that oxygenation can be improved by giving oxygen at a rate of >2 L/min (no target saturation or supporting evidence given).⁶⁶ The American Stroke Association Guideline recommended keeping the oxygen saturation at or above 95% in 2003,²⁴ there was no change to the recommendations in the 2005 update²⁵ of the guideline, but in 2007 the advice was revised to say that oxygen saturation should be maintained at or above 92%.⁶⁷ The latest UK National Clinical Guideline for the management of people with stroke (July 2008)⁶⁸ and the 2008 guidance from the National Institute for Clinical Excellence⁶⁹ state that supplemental oxygen should only be given in people who have had a stroke if the oxygen saturation falls below 95%. None of the recommendations are based on evidence from controlled clinical trials.

Not surprisingly, there is uncertainty amongst physicians treating patients with stroke about which treatment approach to take, and when to give oxygen, as shown by a recent survey of British Stroke Physicians (9).

For all the above reasons it is important to identify groups of patients who benefit from oxygen, and others who do not.

What is the justification for the fixed dose oxygen regime suggested for this study?

A fixed dosage scheme has been chosen to keep the design of the study as simple as possible, so that any recommendations resulting from the study outcome can be carried out in day to day clinical practice.

Ronning and Guldvog have shown that giving oxygen at a rate of 3L/min to all stroke patients during the first 24 hours after hospital admission does not improve overall outcome. They have not reported baseline oxygen saturation, or changes in saturation on treatment. It is therefore possible that some patients were undertreated, and others achieved too high oxygen levels leading to an increase in free radical generation in the ischaemic penumbra (28). There are no other data from clinical studies to inform recommendations for the dose of oxygen to give. The recently updated European Stroke Initiative suggests a dose of 2-4 litres/minute (26), the American Stroke Association Guideline recommends to keep the oxygen saturation at or above 95% (24, 29), but none is based on evidence from controlled clinical trials. In the absence of data to the contrary it is reasonable to assume that treatment should restore oxygen saturation to the normal range.

Normal oxygen saturation for adults is 95-98.5% (30), in healthy older individuals it is lower at 95% \pm 2.5% (31). Oxygen saturation in stroke patients who are normoxic at recruitment is about 1% lower than that of age matched community controls (32). We have just completed a dose titration study for oxygen after acute stroke and found that 2 L/min oxygen by nasal cannula increases oxygen saturation by 2% and 3 L/min by 3% (33). We also found that oxygen masks were less likely to be tolerated than nasal cannulae, leading to poorer treatment compliance with the former. For this study we therefore decided to give oxygen by nasal cannula. A dosage regime of 3 litres per minute for individuals with a baseline oxygen saturation of \leq 93% and 2 L/min for individuals with a baseline saturation >93% is likely to prevent hypoxia without increasing oxygen saturation beyond the upper limit of the normal range.

What are the advantages of giving routine oxygen supplementation at night only?

Patients are more likely to be hypoxic at night

The mean nocturnal oxygen saturation is about 1% lower than awake oxygen saturation, both in stroke patients and controls (32). A recent study done in our unit has shown that a quarter of patients who are normoxic in the day have significant hypoxia during the night. About 60-70% of stroke patients suffer from sleep apnoea early after the stroke (34-36).

The development of hypoxia is more likely to be missed at night

It is more difficult to observe patients in the darkened room, and, unless there are reasons to suspect the patient is unwell, nurses will not waken the patient for routine observations. The development of hypoxia is therefore more likely to be missed at night.

Nocturnal hypoxaemia is more likely to lead to brain tissue hypoxia at night

A recent study in normal volunteers has shown that hypoxaemia leads to a compensatory increase in cerebral blood flow during wakefulness, but not during sleep, and is therefore more likely to result in brain tissue hypoxia at night (37).

Nocturnal oxygen supplementation does not interfere with the patient's daytime mobility

Early mobilisation is an important aspect determining good outcome (2). Patients who are attached to monitoring equipment, or to oxygen supplementation are less likely to be mobilised than patients not attached to such equipment.

Giving routine oxygen at night only might prevent a significant number of otherwise undetected episodes of hypoxia without interfering with the patient's daytime rehabilitation.

5. Study aim and hypothesis

The aim of this study is firstly, to determine which patients will benefit from oxygen after stroke, and secondly to establish whether nocturnal oxygen supplementation is more effective than with continuous oxygen supplementation.

Main Hypothesis

Fixed dose oxygen treatment during the first 3 days after an acute stroke improves outcome after stroke.

Secondary hypothesis

Restricting oxygen supplementation to night time only is more effective than continuous supplementation.

6. Study protocol

Study design

A multi-centre, prospective, randomized, open, blinded-endpoint study of routine oxygen supplementation after acute stroke versus no routine oxygen treatment.

Recruitment

Patients will be recruited from multiple (>30) centres throughout the UK and worldwide. The first study centre to be enrolled will be the University Hospital of North Staffordshire. Centres will be eligible for participation in the study if they admit patients with acute stroke, are able to provide oxygen treatment and monitor oxygen saturation, and if there is a local researcher who will act as the principal investigator for the locality.

Inclusion criteria

All adult patients with an acute stroke will be eligible to be considered for study participation. There are no definite guidelines for oxygen treatment after acute stroke, and there is

uncertainty amongst stroke physicians about who should be given oxygen and for how long. The eligibility criteria for inclusion into the trial reflect this uncertainty, and allow for randomization of all acute stroke patients who do not have definite indications or definite contraindications for oxygen treatment.

Hence adult patients will be eligible for trial inclusion if : They were admitted with symptoms of an acute stroke (e.g. symptom onset within 24 h or less of admission) within the preceding 24 hours, and in the doctor's opinion there is no clear indication for and no clear contraindication against oxygen treatment.

The diagnosis of stroke will be made by history and clinical examination and is at the discretion of the admitting doctor. It will be based on the WHO criteria (rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin) (38). Within the first 24 hours of symptom onset a definite distinction between a stroke and a transient ischaemic attack cannot be made. However, most patients who still have persistent symptoms after one hour will be confirmed to have a stroke. Since waiting for 24 hours for confirmation would unnecessarily delay treatment we omitted the time element from the definition of stroke for the purposes of trial inclusion.

Exclusion criteria

Patients will be excluded from the trial if the responsible doctor considers the patient to have definite indications for or contraindications to oxygen treatment at a rate of 2-3 L/min. The decision will be left to the responsible clinician. This exclusion criterion has been chosen to ensure that all patients are treated according to best medical practice.

Potential indications for oxygen treatment could be: oxygen saturation on air <90%, hypoxia associated with acute left ventricular failure, severe pneumonia, pulmonary embolus, and chronic respiratory failure patients treated with long term oxygen at home.

Potential contraindications to fixed dose oxygen treatment could be type 2 respiratory failure and very severe hypoxia.

Patients will also be excluded if the stroke is not the main clinical problem, or if he/she has another serious life-threatening illness likely to lead to death within the next few months. This group of patients is excluded because it is unlikely that they are going to derive any benefit from the trial treatment.

Intervention

Patients will be randomised into one of 3 treatment groups:

1. Treatment group 1: no routine oxygen supplementation during the first 72 hours after randomisation
2. Treatment group 2: oxygen per nasal cannula over night (21:00-7:00) at a flow rate of 3L/min (if baseline oxygen saturation is 93% or below) or at a flow rate of 2L/min (if baseline oxygen saturation is greater than 93%) during the first 3 nights after randomisation.
3. Treatment group 3: oxygen per nasal cannula continuously (day and night) at a flow rate of 3L/min (if baseline oxygen saturation is 93% or below) or a flow rate of 2L/min (if baseline oxygen saturation is greater than 93%) during the first 72 hours after randomisation.

All patients will have regular observations of vital signs (blood pressure, heart rate, temperature and oxygen saturation) as per the local protocol of the stroke unit, but at least 6-hourly. Treatment of any abnormal findings will be independent of trial allocation. Patients who require oxygen or changes in the dose of oxygen for clinical reasons at any time of the trial will be given the concentration of oxygen they require.

Blinding

This study will be open, since placebo treatment (room air) would have similar side effects as the active treatment (e.g. infection and immobilisation), and would thus bias the data in favour of the treatment group. The main outcomes will be ascertained at 3 months by central follow-up, ensuring that the assessor is blind to the intervention. When the patients complete the questionnaire they may have some vague recollection of being treated with oxygen or not. Patients will be asked to state on the questionnaire if they remember/can guess which treatment group they were in. This will then be compared with the actual allocation to quantify potential bias.

Initial assessment (see case record form)

These will be done by the researcher randomizing the patient and entered on line for patients randomized via the web, and sent to the trial centre by fax for patients randomized via the telephone.

Baseline demographics,
Date and time of event
Glasgow Coma Scale (39)
Predictors of outcome (40)
NIHSS Stroke Scale (41, 42)

Follow-up Assessments

Week 1 (see week 1 follow-up form).

The week one assessment will confirm the diagnosis, document deaths and neurological status (NIHSS), compliance with the intervention, and complications. It will be performed by a member of the local research team trained in the assessment tools 7 days (+/- 1 day to allow for week ends and holidays) after enrolment. In patients who are discharged before the end of 1 week, or who can not be followed at 7 days, the patient will be assessed at discharge and if appropriate the follow-up completed at this time point. Wherever possible we will strive to assess the patient at day 7 after randomisation in hospital or, if discharged, in clinic or in their place of residence as the patient specifies. If 1 week assessment is not possible then the discharge assessment is acceptable as the 1 week outcome. Data will be entered on line or sent to the trial centre via fax.

3 months, 6 months, 12 months (see 3 month, 6 month and 12 month questionnaires)

The main follow-up will be performed centrally at 3 months, a standard procedure for most acute stroke trials. Assessments will be based on a questionnaire sent to the patient's preferred follow-up address by the central team after checking with the GP that the patient is still alive, unless the patient has specified a different preference at the week one assessment. Central follow up will ensure blinding of the assessors to the intervention. For non-responders the address will be checked via the GP and the local researcher and resent. If there is no response the patient will be contacted by phone to see if they preferred personal follow-up or were happy to reply to questions via the telephone. Missing or inconsistent data will be cross-checked with the medical notes, the GP or by personal contact with the patient. For patients who are not contactable via these methods we will determine if they have died and what the cause of death was by requesting information from the Office of National Statistics or the NHS Strategic Tracing Service. The latter will also be contacted if the patient is no longer

resident at the address given, the GP has not seen the patient recently and does not know the contacts of the new address and new GP.

- Deaths (record date and cause of death)
- Discharge status
- Modified Rankin Score (mRS) (43)
- Barthel ADL Score (44)
- Nottingham Extended Activities of Daily Living (EADL) Index (45)
- EuroQuol Score (46-48)
- Memory
- Sleep
- Speech

7. Outcome measures

Primary Outcome

- Modified Rankin Score at 3 months (49)

Secondary outcomes at one week

- No of patients with neurological improvement (≥ 4 point decrease in the NIHSS) (50)
- Any deaths
- Highest oxygen saturation during the first 72 hours
- Lowest oxygen saturation during the first 72 hours

Secondary outcomes at 3 months

- Mortality
- The percentage of patients living at home
- Ability to perform activities of daily living (Barthel index)
- Quality of life (EuroQuol)
- Extended activities of daily living (Nottingham EADL)

Further (explanatory) analyses

- Antibiotic use during week 1
- Sedative use during week 1
- Highest heart rate during the intervention >100
- Highest systolic blood pressure during the intervention > 200 mmHg
- Highest diastolic blood pressure during the intervention > 100 mm Hg
- Oxygen saturation during the intervention
- Percentage of patients describing their memory as 'as good as before the stroke'*
- Percentage of patients describing their sleep as 'as good as before the stroke'*
- Percentage of patients without significant speech problems*
- Change in outcomes over time (repeat 3 month assessments at 6 and 12 months)

*These outcomes have been highlighted as important on the public consultation (51), but are not part of standard assessment scales for stroke outcome.

All study measures will be performed by research staff appropriately trained in the use of the assessment tools.

8. Data management and evaluation

Randomisation

Patients will be randomized using minimised randomisation stratified by well validated prognostic factors (age, sex, living alone, normal verbal component of the Glasgow Coma Scale, ability to lift both arms, ability to walk) (52, 53), routine oxygen treatment during ambulance transfer, and baseline oxygen saturation via a web based randomization system. Randomisation will not be stratified by study centre, because this may result in unacceptably high rates of allocation prediction and selection bias (54). However, retrospective analysis by centre will be performed to investigate and adjust for any heterogeneity of treatment effect by centre.

Data management

The local investigators, their research assistants and data monitors will have access to the patient records. Personalized data (address, telephone number, email, fax) will be kept in the trial office and as electronic copies within each of the centres and at the coordinating centre to allow patients to be contacted for the 3, 6, and 12 month follow-up and to allow data checks and validation.

For all other purposes patient identifiable data will be converted to an alphanumeric code using a specific code number for each patient. The principal investigators, members of the trial steering group, the trial managers, data managers, data monitors, the data analysts/programmers, and the trial statisticians will have access to the anonymised data.

Data will be stored on password protected office computers and on zip discs, flash drives or CD ROMs. At least 3 back up copies will be made of all data. These will be kept in locked cupboards in separate buildings.

Data will be transmitted via Fax, email or the Web from the each local centre to the trial coordinator and data queries will be transmitted via the same route from the trial coordinator to local centres. Anonymised data may be made available to other researchers for meta-analysis and publication in media such as the Cochrane Database.

Statistical analysis

The analysis will be by intention-to treat. The primary outcome is the modified Rankin Scale (mRS) score which has an ordinal range of 0 [best outcome] to 5 [worst outcome]. This will be measured at 3 months (or at the last rating). Deaths will be allocated an arbitrary score of 6 (55). A later primary outcome assessment at 6 months was considered, but rejected because there is a risk of diluting treatment effects by newly occurring health problems unrelated to the trial intervention (56).

The trial tests two hypotheses:

1. Oxygen supplementation results in better (i.e. lower) mRS scores at 3 months than no oxygen.
2. Oxygen at night results in at least as good mRS scores as oxygen given over 24 hours.

It cannot be assumed that any benefits from oxygen will be dose dependent. Oxygen supplementation throughout the 24 hour periods may expose a significant number of patients to oxygen concentrations higher than normal. Being attached to oxygen may also limit mobility and hinder early mobilisation. Oxygen given at night only will provide supplementation at a time when oxygen saturation is lowest in stroke patients, and not interfere with rehabilitation. A prior hypothesis, therefore, is that oxygen at night will have all the potential advantages without disadvantages associated with daytime oxygen use.

The mRS will be compared between two groups using two sample t-tests. These assume a normal distribution and, to test this usually robust assumption, analyses will also be undertaken of the whole ordinal scale (57) by the Mann-Whitney U test using the software StatXact-4 (Cytel, Cambridge Mass.) or an equivalent. Ordinal logistic regression, with possible amalgamation of scores, will be

used to assess the relationship between the mRS at 3 months with treatment groups, baseline oxygen saturation, whether the patient had been given oxygen before randomization or not, the prognostic factors (age, living alone before the stroke, independent pre-stroke, normal verbal response to questions, able to lift the affected arm against gravity, able to walk unaided) (52, 53), the cause of stroke (haemorrhage/infarct), NIHSS score, and TOAST classification. Mortality will be assessed by using survival analysis.

Study size

Many acute stroke studies have been underpowered because the expected treatment effect was unrealistically large (58). While thrombolysis within 3 hours of acute stroke has been shown to lead to moderate clinical benefits (0.5 Rankin point) (55), neuroprotectant treatments may well achieve lesser (e.g. 0.2 Rankin points) treatment effects (59). Because stroke is such a common condition, and oxygen supplementation is inexpensive and universally available, even quite small differences in outcome could have a major impact on the burden of disease. For example, treating 5 patients with an average improvement of 0.2 mRS would improve one patient by one mRS category (e.g. from moderate disability to slight disability). However, though important, small differences do require very large trials to show effectiveness.

The sample size calculation is based on a mean mRS of 3.51 SD 2.03 [blind outcomes of the first 200 patients in the Stroke Oxygen Pilot Study (ISRCTN12362720) (60)]. The sample size allows for a 5% drop-out rate (e.g. retrospective exclusions for change of diagnosis, numbers based on the Stroke Oxygen Pilot study) and a 5% rate of missing outcome data (gives a safe margin, target would be less than 3%).

A sample size of 6000 patients will provide 90% power to detect small (0.2 mRS point) differences between oxygen (continuous and night only groups combined) and no oxygen at $p < 0.01$, and 90% power at $p < 0.05$ to detect small (0.2 mRS point) differences between continuous oxygen and oxygen at night only.

Added 03-10-2012: A sample size of 8000 patients will be used as increasing the recruitment target would give greater power to detect an interaction between subgroups (defined by severity) and the effect of oxygen versus control. The magnitude of the increase in power can be estimated by considering the increase in power to detect the pre-specified odds ratio of 0.83 in the subgroup of 'moderate through to very severe' patients (those with an NIHSS score greater than or equal to 10 and who are more likely to benefit from the treatment); power would rise from 43% to 50%.

9. Ethical Requirements

Approval of the study by the Research Ethics Committee

Multicentre ethical approval has been granted for version 2 of the protocol by the North Staffordshire Research Ethics Committee on 25 June 2008 (COREC 06/Q2604/109).

Good Clinical Practice

The Study will be performed in accordance with the principles stated in the Declaration of Helsinki (61). Study procedures will be guided by the standards outlined in the MRC Guidelines for Good Clinical Practice in Clinical Trials (62).

Patient Information and Consent

Consent will be obtained according to the requirements of the Multicentre Research Committee and the Local Research Ethics Committees before the start of recruitment.

The patient, and where appropriate the next of kin, will be given full and adequate verbal and written information about the nature and purpose of the study, possible risks and benefits. A copy of the patient information sheet and the signed consent/assent will be given to the patient. The patient will be informed that they are free to discontinue participation in the study at any time.

Fully informed consent will be sought from all competent subjects. In patients who are conscious, but not fully competent the information to make a reasoned decision we will provide a simple explanation of the trial and seek the patient's agreement, but also seek assent from the next of kin or from an independent physician.. If an incompetent individual has been included in the trial without giving fully informed consent we will strive to obtain fully informed consent as soon as the patient is able to do so. This will be documented on the week one follow-up form.

The reasons for including patients unable to give fully informed consent:

About one third of stroke patients will have problems with speech and with the understanding of spoken and written material as a consequence of their stroke. It is important to include these patients in the study since they are just as likely to benefit from the treatment as patients who are able to communicate.

It is further important to include as wide a spectrum of stroke patients as possible, in particular patients with severe strokes. Patients with severe strokes may be more likely to develop hypoxia, and may therefore be more likely to benefit from oxygen treatment than patients with mild strokes. However, patients with severe strokes are more likely to be confused, drowsy or dysphasic, and thus unable to give informed consent. Exclusion of subjects unable to give informed consent is thus likely to bias trial outcome. Furthermore, since the group of patients who is unable to consent has different clinical characteristics than patients who can give consent the results of the study may not be applicable to patients with similar clinical presentations to the excluded patients.

Patient/ relatives/ independent clinician information sheets:

The information sheets to be given to patients, relatives, or the independent clinician have been reviewed and edited by users from Strokes R Us (Stoke-on-Trent) and Different Strokes (Coventry).

Monitoring of suspected unexpected serious adverse reactions (SUSARs)

All suspected unexpected serious adverse reactions which are believed to be due to the trial treatment (SUSARs) will be reported as soon as possible within one working day of becoming aware of the event by phoning the study helpline (see contact details on page 5) or by emailing christine.roffe@northstaffs.nhs.uk. A SUSAR report form (<http://www.so2s.co.uk/forms.shtml>) will be completed as fully as possible and sent via fax, see contact details on page 5) to the Chief Investigator and the sponsor [North Staffordshire Combined Healthcare Trust Research and Development, see contact details on page 5]. On this form the patient will be identified by a unique identifying number consisting of the trial identification number (ISRCTN) followed by the number the patient was allocated at randomization. The SUSAR form will be filed in the trial master file and in the case record form. A SUSAR follow-up form will be completed as soon as possible within 5 days of the event and submitted via fax to the numbers above. This will also be filed in the trial master file and the case record form. Unless the event has resolved or a decision has been taken that no further follow-up is required, further follow-up forms will be completed, faxed and filed as outlined above until the event has resolved. Relevant details of the SUSAR and its follow-up will also be recoded in the patient's medical notes. The sponsor will inform the Licensing Authority, the Competent Authorities of any member state in which the trial is being conducted, and the relevant Research Ethics Committee (Research Ethics Committee, Mellor House, Corporation St, Stafford ST16 3SR, Fax 01785 254 640) of the SUSAR as soon as possible no later than 7 days after first becoming aware of the event. The sponsor will provide details of follow-up reports and resolution. The sponsor will also inform all the principal investigators of the trial of the SUSAR. At the end of each year from the start of the trial the sponsor will provide the Licensing authority (Medicines and Healthcare products Regulatory Authority, UK) with a list of all SUSARS relating to the trial during that year and any other

relevant new information relating to the investigational product which may affect the conduct of this trial.

Data protection

Data will be stored and analysed in accordance with national data legislation. Personalised data (address, telephone number, email, fax) will be kept in the trial office and as electronic copies within each of the centres and at the co-ordinating centre to allow patients to be contacted for follow-up and to allow data checks and validation. For all other purposes patient identifiable data will be converted to an alphanumeric code using a specific code number for each patient.

10. Trial Administration

Sponsor

North Staffordshire Combined Healthcare NHS Trust, Harplands Hospital, Hilton Road, Harpfields, Stoke-on-Trent ST4 6TH, Tel 01782 441600 email: fiona.myers@northstaffs.nhs.uk

Person authorized by the sponsor to act on behalf of the sponsor

R&D Director, North Staffordshire Combined Healthcare NHS Trust, Research and Development Department, Directorate of Medicine and Clinical Effectiveness, Harplands Hospital, Hilton Road, Stoke-on-Trent, ST4 6TH. Tel: 01782 441651, E-mail nschsponsor@northstaffs.nhs.uk.

Chief Investigator (CI)

Dr C. Roffe, North Staffs. Combined Healthcare NHS Trust, Holly Lodge, 62 Queens Road, Hartshill, Stoke-on-Trent ST4 7LH. Tel 0300 123 0891 Fax 0300 123 0894, E-mail Christine.roffe@northstaffs.nhs.uk

Trial Management Committee (TMC)

The trial management committee is responsible for the overall design and conduct of the study, analysis of the data, reporting and dissemination of results. It will act on advice of the trial steering committee, the data safety and management committee, the advisory groups and the international advisory committee.

Membership: Dr C. Roffe (chair, stroke physician, clinical lead of the West Midlands Local Stroke Research Network); Prof P Crome (geriatrician, clinical trialist and pharmacologist) Institute for Life Course Studies, Keele University; Prof R Gray (expertise in large clinical trials, director of the Birmingham Clinical Trials Unit) Birmingham University; Prof P Jones (statistician and pro vice chancellor) Keele University, Mr and Mrs Peter and Linda Handy (patient representatives, Strokes R Us, Stoke-on-Trent).

Trial Steering Committee (TSC)

The steering committee will oversee the study. Prof M Dennis will act as independent chairman. Other members are Prof L Kalra (stroke physician, clinical trialist, King's College, London), Prof S Maslin-Prothero (nursing, policy and practice in the NHS, Keele University), J. Daniels (statistician, Birmingham Clinical Trials Unit), Mrs Peta Bell (patient representative, dysphasia Support, Stafford), Prof R Lindley (international advisor, stroke physician, clinical trialist), and members of the TMC.

Data and Safety Monitoring Committee (DMSC)

The remit of the Data Monitoring and Safety Committee will be to ensure that patients are not exposed to unnecessary risks by performing interim safety analyses and to maintain patient safety. If oxygen treatment really provides substantial benefit or harm with respect to the

primary endpoints, then this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge from other sources that oxygen is definitely effective, ineffective, or adverse. To protect against this, during the period of recruitment to the study, interim analyses of major endpoints will be supplied, in strict confidence, to an independent Data Monitoring and Safety Committee (DMSC) along with updates on results of other related studies, and any other analyses that the DMSC may request. The DMSC will advise the chair of the Trial Steering Committee if, in their view, the randomised comparisons in the trial have provided both (a) “proof beyond reasonable doubt” that for all, or for some, types of patient one particular treatment is definitely indicated or definitely contraindicated in terms of a net difference in the major endpoints, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, the exact number of interim analyses is of little importance, so no fixed schedule is proposed. The TSC can then decide whether to close or modify any part of the trial. Unless this happens, however, the Trial Management Group, TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

The DMSC is chaired by Prof. S. Jackson (pharmacology, prescribing, clinical trials). Other members will be Prof. T. Robinson (stroke physician, clinical lead of the Trent Stroke Local Research Network), and Dr S Lewis (statistician).

International Advisory Committee (IAC)

The IAC will advise the steering and management committees on national and international issues relevant to the design and conduct of the trial. There will be a representative for each member state in which the trial is conducted (names and states TBC).

11. References

1. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. The Cochrane Database of Systematic Reviews 2006 Issue 3, John Wiley & Sons, Ltd, Oxford.
2. Indredavik B, Bakke F, Slordahl SA, Rosketh A, Haheim LL. Treatment in a combined acute and rehabilitation stroke unit. *Stroke* 1999;30:917-23.
3. Roffe C. Hypoxaemia and stroke. *Reviews in Clinical Gerontology* 2001;11:323-335.
4. Rowat AM, Dennis MS, Wardlaw JM. Hypoxaemia in acute stroke is frequent and worsens outcome. *Cerebrovasc Dis* 2006; 21:166-172.
5. Lewis LD, Ponten U, Siesjo BK. Homeostatic regulation of brain energy metabolism in hypoxia. *Acta Physiol Scand*. 1973;88:284-6.
6. Nakajima S, Meyer JS, Amano T, Shaw T, Okabe T, Mortel KF. Cerebral vasomotor responsiveness during 100% oxygen inhalation in cerebral ischemia. *Arch Neurol*. 1983;40:271-6.
7. Yager JY, Thornhill JA. the effect of age on susceptibility to hypoxic-ischaemic brain damage. *Neuroscience and Biobehavioural Reviews* 1997;21:167-174.
8. Yamamoto M, Meyer JS, Sakai F, Yamaguchi F. Aging and cerebral vasodilator responses to hypercarbia: responses in normal aging and in persons with risk factors for stroke. *Arch Neurol*. 1980;37:489-96.
9. Arora A, Gray R, Crome P, Roffe C. What do physicians with an interest in stroke consider to be best practice in the diagnosis and treatment of hypoxia after acute stroke? *Br J Cardiol* 2005;12:456-458.
10. Ogburn-Russell L, Johnson JE. Oxygen saturation levels in the well elderly: altitude makes a difference. *J Gerontol Nurs* 1990;16:26-30.
11. Bateman NT, Leach RM. ABC of oxygen. Acute oxygen therapy. *BMJ* 1998;317:798-801.
12. McCord JM. Oxygen-derived free radicals in postischemic tissue injury. *NEJM* 1985;312:159-63.
13. Kontos HA. Oxygen radicals in cerebral ischemia: the 2001 Willis lecture. *Stroke* 2001;32:2712-6.
14. Sugawara T, Fujimura M, Noshita N, Kim GW, Saito A, Hayashi T, Narasimhan P, Maier CM, Chan PH. Neuronal Death/Survival Signalling Pathways in Cerebral Ischemia. *NeuroRx* 2004;1:17-25.
15. Mattson MP, Culmsee C, Yu ZF. Apoptotic and antiapoptotic mechanisms in stroke. *Cell Tissue Res* 2000;301:173-87.
16. Chan PH. Role of oxidants in ischaemic brain damage. *Stroke* 1996;27:1124-1129.
17. Sims NR, Anderson MF. Mitochondrial contributions to tissue damage in stroke. *Neurochem Int* 2002;40:511-26.
18. Crack PJ, Taylor JM. Reactive oxygen species and the modulation of stroke. *Free Radic Biol Med* 2005;38:1433-44.
19. Flynn EP, Auer RN. Eubarc hyperoxemia and experimental cerebral infarction. *Ann Neurol* 2002;52:566-5.
20. Singhal AB, Dijkhuizen RM, Rosen BR, Lo EH. Normobaric hyperoxia reduces MRI diffusion abnormalities and infarct size in experimental stroke. *Neurology* 2002;58:945-52.
21. Rawles JM, Kenmure AC. Controlled trial of oxygen in uncomplicated myocardial infarction. *BMJ* 1976 ;1:1121-3.
22. Ronning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. *Stroke* 1999;30:2033-2037.
23. Singhal AB, Benner T, Roccatagliata L, Koroshetz WJ, Schaefer PW, Lo EH, Buonanno FS, Gonzalez RG, Sorensen AG. A pilot study of normobaric oxygen therapy in acute ischemic stroke. *Stroke*. 2005;36:797-802.

24. Adams HP Jr, Adams RJ, Brott T, del Zoppo GJ, Furlan A, Goldstein LB, Grubb RL, Higashida R, Kidwell C, Kwiatkowski TG, Marler JR, Hademenos GJ; Stroke Council of the American Stroke Association. Guidelines for the early management of patients with ischemic stroke: A scientific statement from the Stroke Council of the American Stroke Association. *Stroke* 2003;34:1056-83.
25. Adams H, Adams R, Del Zoppo G, Goldstein LB; Stroke Council of the American Heart Association; American Stroke Association. Guidelines for the early management of patients with ischemic stroke: 2005 guidelines update a scientific statement from the Stroke Council of the American Heart Association/American Stroke Association. *Stroke* 2005;36:916-23.
26. The European Stroke Initiative Executive Committee and the EUSI Writing Committee. European Stroke Initiative Recommendations for Stroke Management – Update 2003. *Cerebrovasc Dis* 2003;16:311- 337.
27. Royal College of Physicians. National Clinical Guidelines for Stroke. London (2004). <http://www.rcplondon.ac.uk/pubs/books/stroke/index.htm>
28. Ronning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. *Stroke* 1999;30:2033-2037.
29. Khaja AM, Grotta JG. Established treatments for acute ischaemic stroke. *Lancet* 2007;369:319-330.
30. Acid-base balance and blood gases. In: *Clinical Laboratory Diagnosis*. Ed: Thomas L. TH-Books. 1st Ed, Frankfurt 1998.
31. Ogburn-Russell L, Johnson JE. Oxygen saturation levels in the well elderly: altitude makes a difference. *J Gerontol Nurs* 1990;16:26-30.
32. Roffe C, Sills S, Halim M, Wilde K, Allen M, Jones PW, Crome P. Unexpected nocturnal hypoxia in patients with acute stroke. *Stroke* 2003;34:2641-2645.
33. Ali K, Sills S, Roffe C. The effect of different doses and routes of oxygen administration on oxygen saturation in stroke patients. *Neurocritical Care* 2005;3:24-26.
34. Iranzo A, Santamaria J, Berenguer J, Sanchez M, Chamorro A. Prevalence and clinical importance of sleep apnea in the first night after cerebral infarction. *Neurology* 2002;58:911-6.
35. Turkington PM, Bamford J, Wanklyn P, Elliott MW. Prevalence and predictors of upper airway obstruction in the first 24 hours after acute stroke. *Stroke* 2002;33:2037-42.
36. Harbison J, Ford GA, James OFW, Gibson GJ. Sleep-disordered breathing following acute stroke. *Q J Med* 2002; 95:741-747.
37. Meadows GE, O'Driscoll DM, Simonds AK, Morrell MJ, Corfield DR. Cerebral blood flow response to isocapnic hypoxia during slow-wave sleep and wakefulness. *J Appl Physiol*. 2004;97:1343–1348.
38. Aho K, Harmsen P, Hatano S, et al. Cerebrovascular disease in the community: Results of a WHO collaborative study. *Bull World Health Organ* 1980;58:113-130.
39. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974;2:81-83.
40. Weir NU, Counsell CE, McDowall M, Gunkel A, Dennis SM. Reliability of the variables in a new set of models that predict outcome after stroke. *J Neurosurg Psychiatry* 2002;74:447-45.
41. Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, Spilker R, Holleran R, Eberle R, Hertzberg V, Rorick M, Moomaw CJ, Walker M. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989;20, 964-970.
42. Lyden P, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, Haley EC, Grotta J, Marler J. Improved reliability of the NIH Stroke Scale using video training. *Stroke* 1994; 25: 2220-2226.
43. Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gun J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604-7.

44. Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. *Int Disabil Stud.* 1988;10:61-3.
45. Nouri FM, Lincoln NB. An extended Activities of daily living scale for stroke patients. *Clinical Rehabilitation* 1987;1:301-305.
46. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ* 1998;316:736-72.
47. Dorman PJ, Waddell FM, Slattery J, Dennis MS, Sandercock PAG. Is the EuroQol a valid measure of health-related quality of life after stroke? *Stroke* 1997;28:1876-1882.
48. Dorman P, Slattery J, Farrell B, Dennis M, Sandercock P. Qualitative comparison of the reliability of health status assessments with the EuroQol and SF-36 questionnaires after stroke. *United Kingdom Collaborators in the International Stroke Trial. Stroke* 1998;29:63-8.
49. Sulter G, Steen C, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trials. *Stroke.* 1999;30:1538-41.
50. Wityk RJ, Pessin MS, Kaplan RF, Caplan LR. Serial assessment of acute stroke using the NIH Stroke Scale *Stroke* 1994;25:362-5.
51. Ali K, Roffe C, Crome P. What patients want: consumer involvement in the design of a randomized controlled trial of routine oxygen supplementation after acute stroke. *Stroke* 2006;37:865-71.
52. Weir NU, Counsell CE, McDowall M, Gunkel A, Dennis SM. Reliability of the variables in a new set of models that predict outcome after stroke. *J Neurosurg Psychiatry* 2002;74:447-45.
53. SCOPE (Stroke Complications and Outcomes Prediction Engine) Collaborations; IST, Lewis SC, Sandercock PA, Dennis MS. Predicting outcome in hyper-acute stroke: validation of a prognostic model in the Third International Stroke Trial (IST3). *J Neurol Neurosurg Psychiatry* 2008;79:397-400.
54. Hills R, Gray R, Wheatley K. High probability of guessing next treatment allocation with minimisation by clinician. *Controlled Clinical Trials* 2003;24;Suppl 3S:70S.
55. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (NINDS). Tissue plasminogen activator for acute ischaemic stroke. *N Engl J Med* 1995;333:1581-1587.
56. Stroke Therapy Academic Industry Roundtable II (STAIR-II): recommendations for clinical trial evaluation of acute stroke therapies. *Stroke* 2001; 32: 1598-1606.
57. Optimising Analysis of Stroke Trials (OAST) Collaboration, Bath PM, Gray LJ, Collier T, Pocock S, Carpenter J. Can we improve the statistical analysis of stroke trials? *Statistical reanalysis of functional outcomes in stroke trials. Stroke* 2007;38:1911-5.
58. Weaver CS, Leonardi-Bee J, Bath-Hextall FJ, Bath PM. Sample size calculations in acute stroke trials: a systematic review of their reporting, characteristics, and relationship with outcome. *Stroke* 2004;35:1216-24.
59. Lees KR, Zivin JA, Ashwood T, Davalos A, Davis SM, Diener HC, Grotta J, Lyden P, Shuaib A, Hardemark HG, Wasiewski WW; Stroke-Acute Ischemic NXY Treatment (SAINT I) Trial Investigators. NXY-059 for acute ischemic stroke. *N Engl J Med* 2006;354:588-600.
60. Pers. Comm. C. Roffe, P. Jones, S. Sills relating to the Stroke Oxygen Study Pilot.
61. The World Medical Association. Declaration of Helsinki. World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects. Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and as revised by the World Medical Assembly in Tokyo, Japan in 1975, in Venice, Italy in 1983, and in Hong Kong in 1989. <http://www.fda.gov/oc/health/helsinki89.html>
62. Medical Research Council. MRC Clinical Trials Series: MRC Guidelines for Good Clinical Practice in Clinical Trials. London, Medical Research Council, 1998. http://www.mrc.ac.uk/index/publications/publications-ethics_and_best_practice/publications-clinical_trials_guidelines.htm

63. Roffe C, Ali K, Memon I, Pountain S, Sills S, Warusevitane A, Roffe C. The Stoke Oxygen Pilot Study. The effect of routine fixed oxygen supplementation on neurological outcome at one week. *Age Ageing* 2009 [in print].
64. Roffe C, Ali K, Warusevitane A; Pountain S, Jones PW, Crome P. The stroke oxygen pilot study. A randomized controlled trial of routine oxygen supplementation after acute stroke. Outcome at 6 months. *Cerebrovasc Dis* 2009;27(suppl 6):58.
66. European Stroke Organization. Guidelines for the management of ischaemic stroke and transient ischaemic attack. http://www.eso-stroke.org/pdf/ESO08_Guidelines_Original_english.pdf (Accessed 06.02.2009).
67. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi AI, Rosenwasser RH, Scott PA, Wijdicks EF; American Heart Association; American Stroke Association Stroke Council; Clinical Cardiology Council; Cardiovascular Radiology and Intervention Council; Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke* 2007; 38:1655-711.
68. Intercollegiate Stroke Working party. National Clinical Guideline for Stroke, 3rd edition, royal college of Physicians, London, July 2008. <http://www.rcplondon.ac.uk/pubs/contents/6ad05aab-8400-494c-8cf4-9772d1d5301b.pdf> (Accessed 06.02.09)
69. Stroke. Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). National Institute for Health and Clinical Excellence, London, 2008. <http://www.nice.org.uk/nicemedia/pdf/CG68NICEGuidelineWord.doc> (Accessed 06.02.09)