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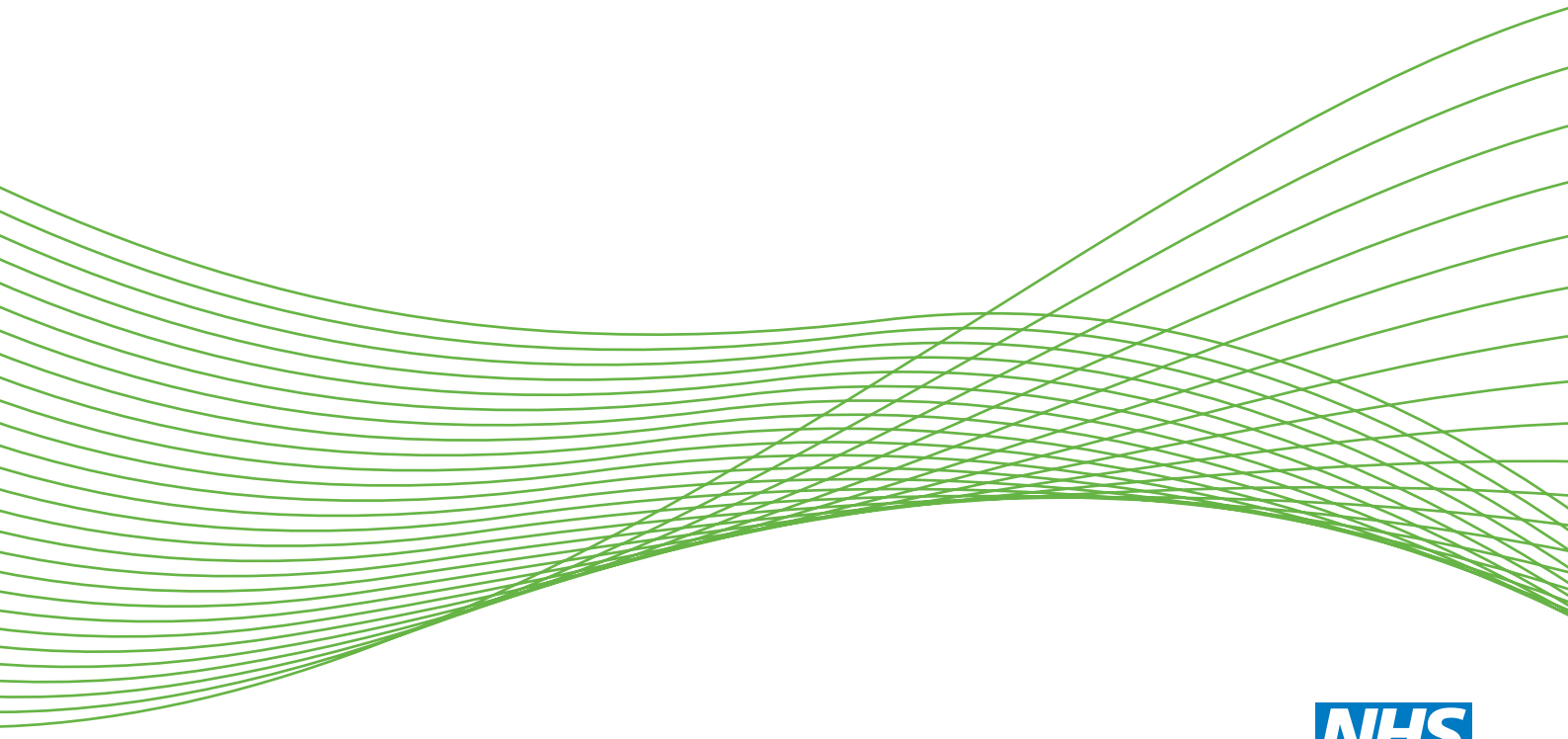

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Routine low-dose continuous or nocturnal oxygen for people with acute stroke: three-arm Stroke Oxygen Supplementation RCT

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Abstract

Routine low-dose continuous or nocturnal oxygen for people with acute stroke: three-arm Stroke Oxygen Supplementation RCT

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Background: Stroke is a major cause of death and disability worldwide. Hypoxia is common after stroke and is associated with worse outcomes. Oxygen supplementation could prevent hypoxia and secondary brain damage.

Objectives: (1) To assess whether or not routine low-dose oxygen supplementation in patients with acute stroke improves outcome compared with no oxygen; and (2) to assess whether or not oxygen given at night only, when oxygen saturation is most likely to be low, is more effective than continuous supplementation.

Design: Multicentre, prospective, randomised, open, blinded-end point trial.

Setting: Secondary care hospitals with acute stroke wards.

Participants: Adult stroke patients within 24 hours of hospital admission and 48 hours of stroke onset, without definite indications for or contraindications to oxygen or a life-threatening condition other than stroke.

Interventions: Allocated by web-based minimised randomisation to: (1) continuous oxygen: oxygen via nasal cannula continuously (day and night) for 72 hours after randomisation at a flow rate of 3 l/minute if baseline oxygen saturation was ≤ 93% or 2 l/minute if > 93%; (2) nocturnal oxygen: oxygen via nasal cannula overnight (21:00–07:00) for three consecutive nights. The flow rate was the same as the continuous oxygen group; and (3) control: no routine oxygen supplementation unless required for reasons other than stroke.

Main outcome measures: Primary outcome: disability assessed by the modified Rankin Scale (mRS) at 3 months by postal questionnaire (participant aware, assessor blinded). Secondary outcomes at 7 days: neurological improvement, National Institutes of Health Stroke Scale (NIHSS), mortality, and the highest and lowest oxygen saturations within the first 72 hours. Secondary outcomes at 3, 6, and 12 months: mortality, independence, current living arrangements, Barthel Index, quality of life (European Quality of Life-5 Dimensions, three levels) and Nottingham Extended Activities of Daily Living scale by postal questionnaire.

Results: In total, 8003 patients were recruited between 24 April 2008 and 17 June 2013 from 136 hospitals in the UK [continuous, $n = 2668$; nocturnal, $n = 2667$; control, $n = 2668$; mean age 72 years (standard deviation 13 years); 4398 (55%) males]. All prognostic factors and baseline characteristics were well matched across the groups. Eighty-two per cent had ischaemic strokes. At baseline the median Glasgow Coma Scale score was 15 (interquartile range 15–15) and the mean and median NIHSS scores were 7 and 5 (range 0–34), respectively. The mean oxygen saturation at randomisation was 96.6% in the continuous and nocturnal oxygen groups and 96.7% in the control group. Primary outcome: oxygen supplementation did not reduce disability in either the continuous or the nocturnal oxygen groups. The unadjusted odds ratio for a better outcome (lower mRS) was 0.97 [95% confidence interval (CI) 0.89 to 1.05; $p = 0.5$] for the combined oxygen groups (both continuous and nocturnal together) ($n = 5152$) versus the control ($n = 2567$) and 1.03 (95% CI 0.93 to 1.13; $p = 0.6$) for continuous versus nocturnal oxygen. Secondary outcomes: oxygen supplementation significantly increased oxygen saturation, but did not affect any of the other secondary outcomes.

Limitations: Severely hypoxic patients were not included.

Conclusions: Routine low-dose oxygen supplementation in stroke patients who are not severely hypoxic is safe, but does not improve outcome after stroke.

Future work: To investigate the causes of hypoxia and develop methods of prevention.

Trial registration: Current Controlled Trials ISRCTN52416964 and European Union Drug Regulating Authorities Clinical Trials (EudraCT) number 2006-003479-11.

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List of abbreviations

BI	Barthel Index
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CT	computerised tomography
CUA	cost–utility analysis
CVA	cerebrovascular accident
EQ-5D-3L	European Quality of Life-5 Dimensions, 3 levels
EQ-VAS	European Quality of Life Visual Analogue Scale
GCS	Glasgow Coma Scale
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
MI	multiple imputation
mRS	modified Rankin Scale
NEADL	Nottingham Extended Activities of Daily Living scale
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio
QALY	quality-adjusted life-year
ROS	routine oxygen supplementation
SD	standard deviation
SO_2S	the Stroke Oxygen Study
SSV	Six Simple Variables
TIA	transient ischaemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment

Plain English summary

Almost one in every six patients dies within the first month of a stroke in the UK. Those who survive are often left with disability and rely on other people to help them with their day-to-day activities. Doctors are still trying to find ways of reducing this level of death and disability. During and after a stroke, blood supply to part of the brain is reduced, leading to a lack of oxygen. This study has looked at whether or not giving patients oxygen soon after their stroke can prevent further brain damage and reduce death and disability.

We recruited 8003 patients from 136 hospitals in the UK. Patients included in the study were randomly assigned to one of three treatment groups: (1) oxygen given continuously for 3 days after their stroke; (2) oxygen given for three nights; or (3) no oxygen, unless it was needed for other reasons. The hospital staff then reviewed the patients' brain function after a week. Patients were sent questionnaires in the post at 3, 6 and 12 months to see how they were doing.

The results have shown that giving oxygen to stroke patients increased the level of oxygen in the blood, but did not improve patients' brain function, level of disability, quality of life or chances of survival. Oxygen treatment did not improve recovery from the stroke.

This means that it is not necessary to give patients oxygen routinely after a stroke unless needed for other reasons.

Scientific summary

Background

The introduction of specialist stroke units has reduced stroke-related mortality and disability. However, stroke is still the largest cause of complex disability, with half of all survivors requiring help with activities of daily living.

Mild hypoxia is not normally a problem in healthy adults, but it is common in stroke patients, and may result in further damage to an already ischaemic brain. Prophylactic oxygen therapy could prevent this additional deterioration by avoiding hypoxic events. However, oxygen treatment is not without side effects. There is an associated risk of infection with the therapy and a patient is confined to bed, impeding early mobilisation and rehabilitation.

Evidence from randomised controlled trials is conflicting, and insufficient to guide clinical practice. This is reflected in clinical uncertainty and conflicting guidelines based on the same evidence. An adequately powered study of routine oxygen supplementation (ROS) is needed to provide reliable information on which recommendations can be based.

Objectives

1. To assess whether or not routine low-dose oxygen supplementation during the first few days following stroke improves patients' outcome compared with no oxygen.
2. To assess whether or not oxygen given at night only is more effective than continuous oxygen.

Methods

The Stroke Oxygen Study (SO_2S) is a multicentre, prospective, randomised, open, blinded-end point (PROBE) trial.

Participants were adult patients with a clinical diagnosis of acute stroke, who were within 24 hours of hospital admission and 48 hours of stroke onset. Patients were not eligible for the trial if they had any definite indications for, or contraindications to, oxygen treatment, or had another serious life-threatening condition that was likely to lead to death within the next 12 months.

Patients were recruited by clinicians and research nurses from 136 hospitals across England, Northern Ireland and Wales. Each hospital had an acute stroke unit. The research team at the recruiting centre randomised the patients via a computer-generated web-based system. Randomisation included a minimisation protocol, which allocated participants on a 1 : 1 : 1 basis to one of three trial arms:

1. Continuous oxygen: oxygen via nasal cannula continuously (day and night) for 72 hours after randomisation. The flow rate was set at 3 l/minute if baseline oxygen saturation was $\leq 93\%$ or 2 l/minute if baseline saturation $> 93\%$.
2. Nocturnal oxygen: oxygen via nasal cannula overnight (21:00–07:00) for three consecutive nights. The flow rate was set at 3 l/minute if baseline oxygen saturation was $\leq 93\%$ or 2 l/minute if the baseline saturation was $> 93\%$.
3. Control group: no ROS during the first 72 hours after randomisation unless required for other clinical reasons.

Patients' vital signs including oxygen saturation were monitored at least 6-hourly. Patients who developed clinical indications for oxygen treatment or needed a higher dose of oxygen than that delivered by the trial intervention were given additional oxygen, as determined by their treating physicians.

Baseline, randomisation and 1-week follow-up data were collected and entered online into the trial database by the research team based at the recruiting hospital. Baseline assessment included patient demographics, date and time of the stroke, oxygen therapy prior to randomisation, existing comorbidities, Glasgow Coma Scale (GCS), the Six Simple Variables (SSV) outcome prediction tool, the National Institutes of Health Stroke Scale (NIHSS) and consent details.

Patients were assessed by members of the local research team at week 1, or on the day of discharge, if sooner. The assessment included neurological function (NIHSS), vital status, adverse events, oxygen prescriptions for clinical indications in addition to the trial intervention, information on compliance, physiological variables, details of other treatments including antibiotics and sedatives, results of computerised tomography or magnetic resonance imaging head scans, the final diagnosis and contact details for follow-up.

The trial co-ordinating centre sent follow-up questionnaires via post to patients at 3, 6 and 12 months post randomisation. If the questionnaires were not returned, then patients or their preferred alternative contacts were telephoned to complete the questionnaire with a data assistant. The questionnaire booklet contained: the discharge date; current living arrangements; hospital readmissions; the modified Rankin Scale (mRS); the Barthel Index (BI); the European Quality of Life-5 Dimensions, three levels (EQ-5D-3L) and the European Quality of Life Visual Analogue Scale (EQ-VAS); the Nottingham Extended Activities of Daily Living (NEADL) scale; patient-reported outcome measures of sleep, eyesight, speech and memory; and which trial treatment they remembered receiving.

The primary outcome was disability assessed by the mRS (range from 0 = no disability to 5 = extreme disability) at 90 days post randomisation. Death was included as a score of 6. Secondary outcomes at day 7 included neurological improvement, NIHSS and mortality, and the lowest and highest oxygen saturations recorded during the 72-hour treatment period. Long-term outcomes were mortality, the number of patients alive and independent, the number of patients living at home, the BI, the EQ-5D-3L and EQ-VAS, and the NEADL, at the 3-, 6- and 12-month time points.

The original sample size calculation of 6000 patients was revised to 8000 patients in October 2012 to give a greater power to detect an interaction between stroke severity subgroups and the effect of oxygen compared with control.

Statistical analysis was by intention to treat. The primary outcome of mRS as a measure of disability at 90 days post randomisation was analysed using an ordinal logistic regression model. Analyses adjusted for age, sex, baseline NIHSS, baseline oxygen saturation and the SSV prognostic index for 6-month independence were also conducted. To avoid bias due to patients dying before the assessment point, the worst outcome on each of the scales was used for the analysis. Planned subgroup analyses were performed for the mRS only, based on a risk stratification approach. The subgroups were based on stroke severity (NIHSS at baseline), baseline oxygen saturation, oxygen treatment prior to randomisation, time since stroke onset, final diagnosis, Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, GCS, age, comorbidities, thrombolysis and baseline SSV risk score for independence at 6 months.

To estimate the cost-effectiveness and cost–utility of ROS versus no oxygen supplementation, a within-trial economic evaluation was conducted. Additional analyses also compared all three trial arms. The cost per additional day of home time gained was calculated for the cost-effectiveness analysis and quality-adjusted life-years (QALYs) for the cost–utility analysis.

Results

Between 24 April 2008 and 17 June 2013, 8003 patients were recruited to SO_2S. Participants were randomised to the three trial arms, with 2668 in the control group, 2668 in the continuous oxygen group and 2667 in the nocturnal (night-time only) oxygen group.

Fully informed consent was given by 6991 (87%) of patients and assent given by a relative, carer or independent legal representative for 1012 (13%) patients. In total, over the 12-month participation, 89, 81 and 81 patients withdrew from the continuous oxygen, nocturnal oxygen and control groups, respectively.

Baseline characteristics were well balanced across the three trial arms. The overall mean age was 72 years [standard deviation (SD) 13 years] and 4398 (55%) patients were male. Of the 8003 patients, 7332 (92%) were independent in activities of daily living prior to their stroke, and this was equally distributed across the three groups. Medical history and comorbidities were also well matched, with ischaemic heart disease ($n = 1602$, 20%), heart failure ($n = 657$, 8%), atrial fibrillation ($n = 1995$, 25%) and chronic lung conditions ($n = 812$, 10%) recorded in each group. The median GCS score was 15 [interquartile range (IQR) 15–15] and the mean and median NIHSS scores were 7 and 5 (range 0–34), respectively. Ischaemic stroke was the final diagnosis in 82% of patients ($n = 6555$), followed by primary intracerebral haemorrhage in 7% ($n = 588$), transient ischaemic attack in 2% ($n = 168$), and a non-stroke diagnosis in 4% ($n = 292$). This information was unavailable for 106 patients (1%). The mean baseline oxygen saturation was 96.6% in the continuous (SD 1.7) and nocturnal oxygen (SD 1.6) groups and 96.7% (SD 1.7) in the control group. Oxygen therapy prior to randomisation was recorded in 20% of patients.

In the continuous oxygen arm 2158 (81%) patients completed the 72 hours of the trial intervention and 433 (16%) did not. Treatment adherence was similar in the nocturnal oxygen arm, with 2225 (83%) patients completing the three nights of oxygen therapy and 361 (14%) not doing so. Discharge from hospital was the most common reason for a patient not receiving the complete trial intervention. In the control group 2229 (84%) patients did not receive any ROS for the treatment of stroke. There were 23 (1%) patients who received oxygen therapy in the control group. This information was missing for 406 (15%) participants.

Routine oxygen supplementation did not improve functional outcome at 3 months compared with the control group. No statistically significant difference was recorded between the continuous oxygen and the nocturnal oxygen arms. The unadjusted odds ratio (OR) for a better outcome (lower mRS) was 0.97 [95% confidence interval (CI) 0.89 to 1.05; $p = 0.5$] for oxygen (continuous and nocturnal combined) compared with the control, and 1.03 (95% CI 0.93 to 1.13; $p = 0.6$) for continuous compared with nocturnal oxygen. The adjusted analyses yielded very similar results. For combined oxygen compared with control the OR was 0.97 (95% CI 0.89 to 1.06; $p = 0.5$) and comparing the two oxygen interventions the OR was 1.01 (95% CI 0.92 to 1.12; $p = 0.8$). No subgroups were identified that benefited from oxygen supplementation when the study population was divided based on the previously described parameters. Sensitivity analyses based on multiple imputation and an adherers-only analysis, aimed at investigating potential bias resulting from missing data, also revealed similar outcomes. Additional sensitivity analyses represented best- and worst-case scenarios, to set maximum plausible bounds for the effect of missing data.

Neurological improvement at week 1 did not differ between the three trial groups (median NIHSS score, 2; IQR, 1–6). Exploratory analyses of the data collected at the week 1 review did not show any appreciable differences for indicators of stress (highest heart rate, blood pressure and need for sedation), or for indicators of infection (antibiotic treatment and highest temperature). Highest and lowest oxygen saturations increased by 0.8% and 0.9%, respectively, in the continuous oxygen group when compared with the control group and by 0.5% and 0.4%, respectively, when compared with the nocturnal group ($p < 0.001$ for all comparisons). Significantly more participants in the combined oxygen group than in the control group required oxygen for clinical reasons outside the trial intervention ($p = 0.0008$). This was also the case in the continuous versus nocturnal oxygen groups ($p = 0.03$).

Long-term functional outcome did not improve with oxygen therapy at any of the 3-, 6- and 12-month follow-up time points. The number of patients who were alive and independent and back in their own homes, the ability to perform basic activities of daily living (BI) or the Nottingham Extended Activities of Daily Living scale score and quality of life (EQ-5D-3L) at 90, 180 and 365 days were not increased by ROS. Mortality at 90 days was similar in the oxygen (both groups combined) and control group (hazard ratio 0.97, 99% CI 0.78 to 1.21; $p = 0.8$), and for continuous oxygen versus oxygen at night only (hazard ratio 1.15, 99% CI 0.90 to 1.48; $p = 0.1$). Neither patient-reported outcome measures nor the rate of readmission to hospital was improved by the trial interventions at any of the follow-up assessments. The number of serious adverse events did not differ at any of the three follow-up time points between the three trial arms.

The health economics analysis results were in line with the clinical findings. The trial treatment was associated with increased costs, as expected. Patients did not return home more quickly or experience more QALYs with either of the oxygen treatments. The cost-effectiveness analysis demonstrated a low probability of cost-effectiveness (31%) at £20,000/QALY.

Conclusions

The results of the study have shown that low-dose oxygen supplementation in stroke patients who are not severely hypoxic does not confer any benefits either for the whole population or for any subgroups. This lack of benefit is consistent across all outcomes and for all time points up to 1 year. It also did not matter if the oxygen was given continuously or at night-time only. Future research should investigate the causes of hypoxia and explore ways of preventing desaturations in stroke patients.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN52416964 and European Union Drug Regulating Authorities Clinical Trials (EudraCT) number 2006-003479-11.

Funding

This project was funded by the National Institute for Health Research (NIHR) Research for Patient Benefit and Health Technology Assessment programmes and will be published in full in *Health Technology Assessment*; Vol. 22, No. 14. See the NIHR Journals Library website for further project information.

Chapter 1 Introduction

Stroke is the third most common cause of death worldwide.[1] With approximately 110,000 strokes per annum in England, it accounts for 11% of deaths.[2] Stroke mortality is cited as 20–30% within 1 month in the 2007 National Stroke Audit report.[2] More recent data suggest lower rates: between 14% and 17% for the UK[3] and 14.5% in the USA.[4] Improvements in processes of care have significantly contributed to this reduction.[4] However, half of all stroke survivors are left dependent on others for everyday activities,[2] making stroke the largest cause of complex disability.[5] Care on specialist stroke units has been shown to reduce death and disability significantly.[6] It does, however, remain unclear which aspects of stroke care are crucial for improving outcome. Prevention and treatment of hypoxia could potentially be one of the reasons for better outcome with specialist stroke care.

Scientific background

Prevalence of hypoxia and effects on outcome

Mild hypoxia is common in stroke patients and may have significant adverse effects on the ischaemic brain.[7] Hypoxia with oxygen saturations falling below 92% has been observed in 24% of continuously monitored stroke patients within the first 24 hours of symptom onset.[8] While healthy adults with normal cerebral circulation can compensate for mild hypoxia by an increase in cerebral blood flow,[9] this is not possible in the already ischaemic brain after stroke.[10–13] Hypoxaemia with oxygen saturations falling below 90% in the first few hours after hospital admission is associated with a doubling of mortality[14] and a trebling of the rate of institutionalisation.[15] Patients on a stroke unit are more likely to receive oxygen than patients on a non-specialised general ward[16] and less likely to be hypoxic.[17] An observational study of processes of care has shown that hypoxia increases the risk of an adverse outcome fivefold if only some of the hypoxic episodes are treated with oxygen, but has no adverse effect on outcome if all episodes of hypoxia are treated with oxygen.[15] Prophylactic oxygen treatment could prevent hypoxia and secondary neurological deterioration.

Potential adverse effects of oxygen treatment

However, oxygen treatment is not without side effects.[18] 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,[19–22] especially during reperfusion. Marked changes in adenosine triphosphate 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. Ischaemia-induced decreases in the mitochondrial capacity for respiration result in reduced oxygen consumption and further increase free radical generation during reperfusion.[23] Oxidative stress has also been implicated in the activation of cell signalling pathways, which leads to apoptosis and neuronal cell death.[24,25] While much research points towards adverse effects of hyperoxia in the ischaemic brain, there is also evidence to support the notion that therapy-induced eubaric hyperoxia may be neuroprotective.[19,20,26,27] Routine oxygen supplementation (ROS) for acute myocardial infarction has been abandoned after a clinical trial showed no benefit and potential harm.[28]

Randomised controlled trials of oxygen treatment after acute stroke

Evidence from randomised controlled trials of oxygen supplementation after acute stroke is conflicting and insufficient to guide clinical practice. A quasi-randomised study of oxygen supplementation for acute stroke by Rønning and Guldvog[29] 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.[29] A very small ($n = 16$) 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 compared with 17% of control patients ($p = 0.06$) but no long-term clinical benefit at 3 months.[30] In the Stroke Oxygen Pilot Study (ISRCTN 12362720), the flow rate of oxygen was lower (2 or 3 l/minute dependent on baseline oxygen saturation) and treatment was continued for longer (72 hours). Neurological recovery at 1 week was better in the oxygen group than in the control group.[31] While there was no difference in the mRS at 6 months, there was a trend for better outcome with oxygen after adjustment for differences in baseline stroke severity and prognostic factors.[32] In contrast to the earlier study by Rønning and Guldvog,[29] oxygen was as effective in mild as in severe strokes. These results are promising, but need to be confirmed in a larger study.

Recommendations for oxygen treatment in national and international clinical guidelines

Clinical guidelines for oxygen supplementation after stroke are not based on evidence from randomised clinical trials, and have changed over time without obvious reason. The European Stroke Organization (2008)[33] stated that ROS to all stroke patients had not been shown to be effective, but that adequate oxygenation was important, and that oxygenation can be improved by giving oxygen at a rate of > 2 l/minute (no target saturation or supporting evidence given). In 2003, the American Stroke Association Guideline[34] recommended keeping the oxygen saturation at or above 95%. The 2005 update[25] of the guideline made no change to the recommendations. In 2007, the advice was revised to say that oxygen saturation should be maintained at or above 92%,[35] but in 2013 the Association reverted to recommending maintenance of an oxygen saturation at or above 95%.[36] In the UK, the National Clinical Guideline for the management of people with stroke recommended keeping oxygen saturation within normal limits in 2005 and in 2008[37,38] and in 2012[39] it specified that this means maintaining an oxygen saturation ≥ 95%. None of the recommendations is based on evidence from controlled clinical trials. A survey of British stroke physicians showed that there is uncertainty among physicians treating patients with stroke about which treatment approach to take, and when to give oxygen.[40]

Rationale for the Stroke Oxygen Study

Hypoxia is common after acute stroke and is associated with worse outcomes. Prevention of hypoxia could avert secondary brain damage and improve recovery. Evidence from randomised controlled trials is conflicting, and insufficient to guide clinical practice. This is reflected in clinical uncertainty and conflicting guidelines based on the same evidence. An adequately powered study of ROS is needed to provide reliable information on which recommendations can be based.

Aims

The aim of the Stroke Oxygen Study (SO_2S) is, first, to establish whether or not ROS will improve outcome after stroke and, second, to determine whether or not oxygen given at night only is more effective than oxygen given continuously.

Rationale for the fixed dose oxygen regimen used in the Stroke Oxygen Study

A fixed dosage scheme was 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.

Rønning and Guldvog[29] have shown that giving oxygen at a rate of 3 l/minute to all stroke patients during the first 24 hours after hospital admission does not improve overall outcome. They did not report baseline oxygen saturation, or changes in saturation on treatment. It is therefore possible that some patients were undertreated, and that others achieved too high oxygen levels, leading to an increase in free radical generation in the ischaemic penumbra. There were no other data from clinical studies to inform recommendations for the dose of oxygen to give for routine supplementation at the time the study was designed. The European Stroke Organization suggested a dose of 2–4 l/minute and the American Stroke

Association Guideline recommended keeping the oxygen saturation at or above 95%,[34,41,42] but these recommendations were not based on evidence from controlled clinical trials. In the absence of data to the contrary, it was reasonable to assume that treatment should restore oxygen saturation to the normal range.

Normal oxygen saturation in adults is 95–98.5%,[43] in healthy older individuals it is reported to be lower, at 95% [standard deviation (SD) 2.5%].[44] Oxygen saturation in stroke patients who are normoxic at recruitment is about 1% lower than that of age-matched community control patients.[45] We have conducted a dose titration study for oxygen after acute stroke and found that 2 l/minute oxygen by nasal cannula increases oxygen saturation by 2% and 3 l/minute by 3%.[46] 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 regimen of 3 l/minute in individuals with a baseline oxygen saturation of $\leq 93\%$ and 2 l/minute in individuals with a baseline saturation $> 93\%$ was therefore considered likely to prevent hypoxia without increasing oxygen saturation beyond the upper limit of the normal range.

Rationale for 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 in both stroke patients and control patients.[45] This study has also 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 stroke.[47–49]

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 do not usually wake 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 study in healthy 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.[50]

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

Early mobilisation is an important aspect determining good outcome.[16] 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 may prevent a significant number of otherwise undetected episodes of hypoxia without interfering with the patient's daytime rehabilitation.

Chapter 2 Methods

Trial design

The Stroke Oxygen Study is a multicentre, prospective, randomised, open, blinded-end point (PROBE) trial. For this controlled, single-blind, parallel group trial patients were randomised in a 1 : 1 : 1 ratio to one of three study arms:

1. continuous oxygen supplementation
2. nocturnal oxygen supplementation only
3. no ROS, unless required for clinical reasons other than stroke.

Both the Stroke Oxygen Study protocol and the statistical analysis plan have been published in an open-access journal.[51,52]

Hypothesis

The main hypothesis was that fixed low-dose oxygen treatment during the first 3 days after an acute stroke improves outcome compared with no oxygen.

The secondary hypothesis was that restricting oxygen supplementation to night-time only is more effective than continuous supplementation.

Participants

Recruitment

Patients were recruited by research nurses and clinicians from 136 hospitals (secondary care) across England, Northern Ireland and Wales (see *Appendix 1* for a list of recruiting centres). All recruiting hospitals had acute stroke units, were able to carry out the required observations four times a day and had a stroke-trained principal investigator. Screening, baseline, randomisation and 1-week follow-up data were collected and entered online into the trial database by the research staff based in the local hospital.

Inclusion criteria

- Adult patients (aged ≥ 18 years) with clinical diagnosis of acute stroke.
- Within 24 hours of hospital admission.
- Within 48 hours of stroke onset.

Exclusion criteria

- Definite indication or contraindication to oxygen treatment at a rate of 2–3 l/minute.
- Stroke not the main clinical problem or patient has another serious life-threatening illness likely to lead to death within the next 12 months.

Consent

Fully informed consent was sought from all research participants. Research nurses or clinicians explained the study to potential participants, who were also given a patient information sheet explaining the trial. Owing to the acute nature of stroke and the intervention being tested, there was not a 24-hour consideration period between receiving the information and taking informed consent. In patients who were unable to give fully informed consent, assent was sought from either the patient's next of kin or from an independent physician.

Fully informed consent was obtained in patients who regained capacity during the first week following randomisation.

Interventions

Patients were randomised to one of the following three groups:

- Continuous oxygen: oxygen via nasal cannula continuously (day and night) for 72 hours after randomisation. The flow rate was set at 3 l/minute if baseline oxygen saturation was ≤ 93% or 2 l/minute if baseline saturation > 93%.
- Nocturnal oxygen: oxygen via nasal cannula overnight (21:00–07:00) for three consecutive nights. The flow rate was set at 3 l/minute if baseline oxygen saturation was ≤ 93% or 2 l/minute if baseline saturation > 93%.
- Control group: no ROS during the first 72 hours after randomisation unless required for other clinical reasons.

The oxygen used for the trial was supplied by the hospital through either wall-mounted sockets or portable or stationary oxygen bottles, depending on local practice.

Follow-up

Patients were followed up at 1 week by research staff at the recruiting hospital, and then at 3, 6 and 12 months via a postal questionnaire from the trial co-ordinating centre (*Figure 1*). The case report form is presented in *Appendix 2.*

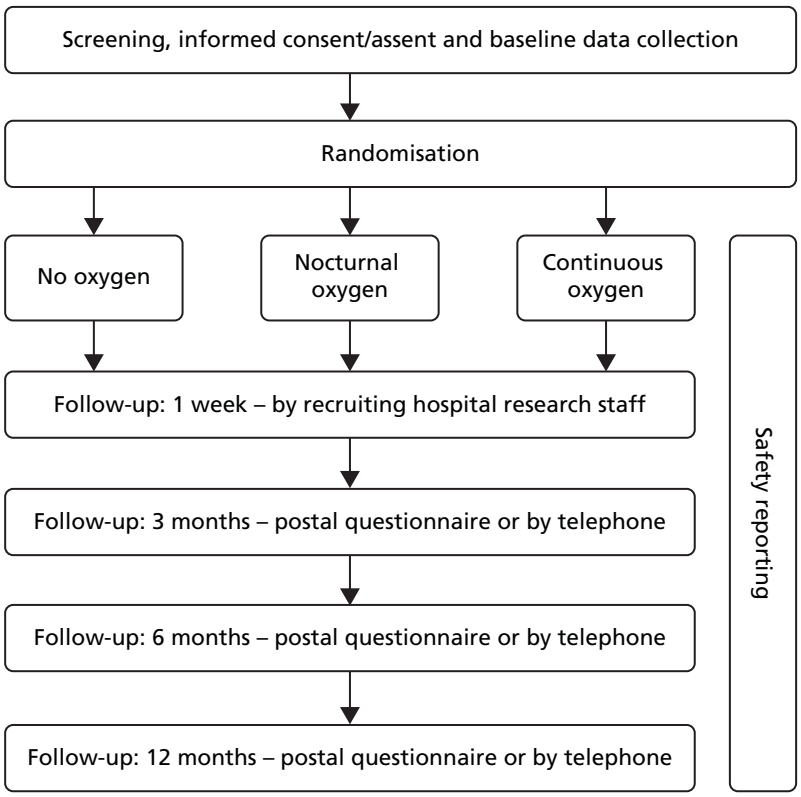

FIGURE 1 Trial design.

Assessments

See *Table 1* for a summary of patient assessments and timings.

TABLE 1 Summary of patient assessments

Outcome measure	Screening	Baseline	Week 1	3 months	6 months	12 months
Eligibility	✓					
Demographics		✓				
Glasgow Coma Scale		✓				
Medical history		✓				
Oxygen treatment prior to randomisation		✓				
Prognostic factors (SSV)		✓				
NIHSS (neurological function)		✓	✓			
Antibiotics, antipsychotics and sedatives during week 1			✓			
Highest blood pressure and highest heart rate during first 72 hours			✓			
Oxygen saturation during first 72 hours			✓			
Compliance with oxygen/control treatment			✓			
CT/MRI diagnosis			✓			
Final diagnosis			✓			
Date of discharge (when appropriate)			✓	✓	✓	✓
Discharge location[a]			✓			
TOAST classification			✓			
Modified Rankin Scale (disability)			✓[b]	✓	✓	✓
Adverse events			✓	✓	✓	✓
Living arrangements				✓	✓	✓
Hospital readmissions				✓	✓	✓
Barthel Index (activities of daily living)				✓	✓	✓
EQ-5D-3L (quality of life)				✓	✓	✓
NEADL				✓	✓	✓
Patient-reported outcome measures (memory, sleep, eyesight and speech)				✓	✓	✓
Participants' awareness of trial allocation				✓	✓	✓
Who completed the follow-up questionnaire				✓	✓	✓
Co-recruitment with other trials			✓	✓	✓	✓

CT, computerised tomography; EQ-5D-3L, European Quality of Life-5 Dimensions, three levels; MRI, magnetic resonance imaging; NEADL, Nottingham Extended Activities of Daily Living scale; NIHSS, National Institutes of Health Stroke Scale; SSV, Six Simple Variables; TOAST, Trial of Org 10172 in Acute Stroke Treatment.
a Discharge location recorded in 125 patients.
b Modified Rankin scale only recorded in 267 patients.

Baseline assessment

This was done by the research team randomising the patient, and was either entered online for patients randomised via the web or sent to the trial centre by fax for patients randomised via telephone. The initial assessment included baseline demographics, date and time of the event, whether or not the patient had been given oxygen in the ambulance or in the emergency department, and how much, comorbidities [chronic obstructive pulmonary disease, other chronic lung problems, heart failure (congestive cardiac failure), ischaemic heart disease, and atrial fibrillation], the Glasgow Coma Scale (GCS) score,[53] score on the Six Simple Variables (SSV) outcome predictor tool,[54] the National Institutes of Health Stroke Scale (NIHSS) score,[55,56] the type of consent (by patient or legal representative) and the date and time of randomisation.

Week 1 assessment

The week 1 assessment was performed by a member of the local research team trained in the assessment tools at 7 days (± 1 day) after enrolment. In patients who were discharged before the end of 1 week, or who could not be followed at 7 days, the assessment was conducted at discharge. Data were entered online or sent to the trial centre via fax. The week 1 assessment included neurological function (NIHSS), vital status, adverse events, whether or not the patient was prescribed oxygen for clinical indications during the first 72 hours, information on compliance with the treatment, details of other treatments (antibiotics during week 1, thrombolysis, sedatives or antipsychotics), physiological variables (highest heart rate, highest systolic and diastolic blood pressure, highest and lowest oxygen saturation during the first 72 hours, and the highest temperature during week 1), the result of the computerised tomography (CT) or magnetic resonance imaging head scan (cerebral infarct/primary intracerebral haemorrhage/subdural haemorrhage/brain tumour/head scan not performed/other), the final diagnosis [ischaemic stroke/transient ischaemic attack (TIA)/primary intracerebral haemorrhage/cerebrovascular accident (CVA) without CT confirmation of aetiology/other], and the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification of stroke aetiology.[57] Compliance was assessed by asking whether or not oxygen was prescribed on the drug chart, whether or not it was signed, and whether or not it was stopped before the end of 72 hours. After an amendment of the case report form [version 1, amendment 3 (30 August 2009)], additional details were recorded for the final 4143 patients. These included a more in-depth assessment of compliance with a record of oxygen saturation at 06:00, 12:00 and 00:00, whether or not oxygen treatment was in place at 06:00 and 00:00; whether or not the patient had been enrolled into another study, and which, the pre-stroke modified Rankin Scale (mRS) and the European Quality of Life-5 Dimensions, three levels (EQ-5D-3L), whether or not this was reported by the patient or a relative, discharge destination (if discharged), and whether or not a new brain haemorrhage was identified on a second CT of the head (if conducted).

Three-, 6- and 12-month assessments

The 3-, 6- and 12-month follow-up assessments were performed centrally by the Stroke Oxygen Study team. Following a call to the participant's general practitioner to confirm that the participant was alive and the contact details were the same as those on the trial database, postal questionnaires were sent to all participants at 3, 6 and 12 months post randomisation. The questionnaires contained the discharge date, the mRS,[58] the Barthel Index (BI),[59] the EQ-5D-3L and the EQ-VAS,[60–62] the Nottingham Extended Activities of Daily Living scale (NEADL),[63] questions regarding current abode, whether or not the patient had been readmitted to hospital since the stroke, patient-reported outcome measures (sleep, speech and memory), and a question on whether or not they remembered which treatment they were randomised to. If the questionnaire was not returned within a few weeks, a data assistant at the trial co-ordinating centre telephoned the patient and completed the questionnaire over the telephone with either the patient or a relative/carer. See *Table 1* for a summary of all patient assessments and timings.

Outcomes

Primary outcome

The primary outcome measure was disability assessed by the mRS at 90 days post randomisation.[58,64] The mRS is an ordinal scale that ranges from 0 for a patient with no disability to 5 for extreme disability. Death was included in the scale as a score of 6.

Secondary outcome measures at 1 week

The number of patients with neurological improvement (≥ 4-point decrease from baseline in the NIHSS score or a value of 0 at day 7),[55,56] NIHSS score, mortality, the lowest and highest oxygen saturation during the 72-hour treatment period and the number of patients whose oxygen saturation fell below 90% were all secondary outcome measures.

Secondary outcome measures at 3, 6 and 12 months

Mortality, the number of patients alive and independent (mRS score of ≤ 2), the number of patients living at home, the BI of activities of daily living, quality of life EQ-5D-3L and European Quality of Life Visual Analogue Scale (EQ-VAS) and the NEADL index were all secondary outcome measures for 3-, 6- and 12-month time points.

Sample size

The original sample size calculation of 6000 patients was based on a mean mRS score of 3.51 (SD 2.03). These values came from the first 200 patients in the Stroke Oxygen Pilot Study.[32] A 5% dropout rate was assumed, along with 5% missing outcome data, giving a total of 10% lost to follow-up. The sample size of 6000 patients provided 90% power to detect small (0.2 mRS point) differences between ROS (continuous and nocturnal groups combined) and no oxygen (control group) at a p-value of ≤ 0.01 and 90% power at a p-value of ≤ 0.05 to detect small (0.2 mRS point) differences between continuous and nocturnal oxygen supplementation.

The sample size calculation was revised in October 2012 without any knowledge of interim results. Recalculation was conducted using ordinal methods to match with the Statistical Analysis Plan. The study size was subsequently consequently revised to 8000 patients. Protocol version 2 amendment 4 (18 October 2012) gave greater power to investigate any differential effectiveness of oxygen compared with control within subgroups, in particular those with more severe disease.

Randomisation and allocation

Patients were randomised via a computer-generated web-based randomisation system at the Birmingham Clinical Trials Unit. Randomisation was performed using minimisation with the following factors: the SSV prognostic index for independent survival at 6 months (cut-off points ≤ 0.1, > 0.1 to ≤ 0.35, > 0.35 to ≤ 0.70 and > 0.70), oxygen treatment before randomisation (yes, no and unknown), baseline oxygen saturation on air (< 95% and ≥ 95%), and time since stroke onset (≤ 3 hours, > 3 to ≤ 6 hours, > 6 to ≤ 12 hours, > 12 to ≤ 24 hours and > 24 hours). Study centre was not included as a minimisation variable to avoid potentially high rates of allocation prediction and selection bias. Patients were randomised via a web-based randomisation program at the level of the individual on a 1 : 1 : 1 basis to either no oxygen, nocturnal oxygen or continuous oxygen. Enrolment and intervention assignment was performed by the clinical team at the recruiting centre.

Blinding

This study was open, as placebo treatment (room air) would have similar side effects as the active treatment (e.g. infection and immobilisation), but no potential benefit, and could thus bias the data in favour of the treatment group. The main outcomes were ascertained at 3 months by central follow-up, which ensured that the assessor was blind to the intervention. Assessment was by postal questionnaire, or, when participants did not respond to the letters, by telephone interview. It is possible that the patients completing the follow-up questionnaire or responding to the interview questions may have had some recollection of being treated with oxygen or not. Patients were asked to state on the questionnaire if they remembered/could guess which treatment group they were in. This was compared with the actual allocation to quantify potential bias.

Statistical methods

The analysis is by intention to treat. The primary outcome measure is disability (mRS) at 90 days after randomisation. The mRS is an ordinal scale ranging from 0 (no disability) to 5 (extreme disability). Patients who were classified as dead at the 3 months were allocated a mRS score of 6, thus creating a 0 to 6 scale.

The mRS was analysed using an ordinal logistic regression model. Both an unadjusted (primary) and adjusted (secondary) analysis were performed. For each outcome variable, the unadjusted analysis is the primary analysis and the covariate-adjusted analysis is the secondary analysis. Adjusted analyses incorporated the following covariates: age, sex, baseline NIHSS score, baseline oxygen saturation and the SSV prognostic index for 6-month independence. For analysis of mortality data, the prognostic index for 30-day survival was used in place of that for 6-month independence.

Participants who died before the assessment point did not have data for NIHSS, BI, EQ-5D and EQ-VAS, or NEADL. To avoid bias in favour of the treatment arm with higher mortality (should this be the case), death was included in the analysis of the NIHSS, BI, EQ-VAS and the NEADL as the worst outcome on the scale.[65]

For continuous outcomes means and SDs or medians and interquartile ranges (IQRs) are reported, as appropriate. Unadjusted analyses used an unrelated *t*-test, with the mean difference between treatments and corresponding confidence interval (CI) reported. In the event of major deviations from the assumptions of the *t*-test, an appropriate alternative analysis was used. The adjusted analysis used analysis of covariance methods, with the covariates specified earlier included in the analysis.

For dichotomous outcomes, percentages were compared across the treatment comparisons using a chi-squared test (unadjusted analysis). The adjusted analysis of dichotomous outcomes used binary logistic regression with the covariates listed earlier. Odds ratios (ORs) and CIs are reported. The number needed to be treated was to be calculated, if significant effects were to be seen.[66] As there were no differences, this was not done.

For ordinal secondary outcomes, the analyses described for the mRS were applied.

Data at 6 and 12 months

The longer-term follow-up data at 6 and 12 months were analysed at each time point using the same methods as those listed previously. In addition, analyses were performed across 3-, 6- and 12-month time points using a longitudinal repeated measures analysis, in this case linear mixed models.[67]

The treatment effect was initially assumed to be constant over time; further analyses were carried out to investigate the effects of including time and a treatment-by-time interaction in the models.

Mortality was analysed using log-rank methods (unadjusted analysis) with Kaplan–Meier plots. The adjusted analysis used Cox regression methods, including the covariates listed above. In the covariates, the prognostic index for 30-day survival replaced that for independence at 6 months. The proportional hazards assumption associated with the Cox regression was tested via Schoenfeld residuals. Hazard ratios and 95% CIs are reported for both the unadjusted and adjusted analyses.

Planned subgroup analyses

These were performed in respect of the primary outcome measure only, based on a risk-stratification approach.[68] The subgroups comprise:

- NIHSS score at baseline as indicator of stroke severity (0–4, 5–9, 10–14, 15–20 and > 20)
- baseline % oxygen (O_2) saturation (< 94%, 94–94.9%, 95–97% and > 97%)
- treatment with O_2 prior to randomisation (yes/no)
- time in hours since onset of stroke (< 4 hours, 4 to < 7 hours, 7 to < 13 hours, 13 to < 24 hours and ≥ 24 hours)
- final diagnosis (haemorrhage, infarct, TIA and other)
- TOAST classification of infarct aetiology
- GCS score (motor plus eye score:< 10 and 10)
- age (< 50 years, 50–80 years and > 80 years)
- history of chronic obstructive airway disease or asthma (yes/no)
- history of heart failure (yes/no)
- thrombolysed (yes/no)
- baseline SSV risk score for independence at 6 months (≤ 0.1, > 0.1 to 0.35, > 0.35 to 0.7 and > 0.7).

These subgroup effects were analysed by means of an interaction term;[69] however, pairwise hypothesis tests between the levels of the subgroup factor were not performed owing to the likely low level of statistical power. Subgroup-specific estimates are reported descriptively with 99% CIs and displayed graphically on a forest plot.

Health economics methods

Overview

A within-trial economic evaluation was conducted alongside the clinical trial in order to estimate the cost-effectiveness and cost–utility of ROS compared with no oxygen supplementation (no ROS) after stroke, over 12 months' follow-up. Further analysis compared all three trial arms: (1) no ROS, (2) nocturnal oxygen for three nights, and (3) 72 hours' continuous oxygen. The base-case economic evaluation adopted an NHS/Personal Social Services perspective. The cost-effectiveness analysis calculated the cost per additional day of home time gained, using information on length of stay in hospital and discharge destination. The cost–utility analysis (CUA) used quality-adjusted life-years (QALYs) as the benefit measure, in which QALYs take into account the survival and quality of life of an individual. The reporting of this analysis follows the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[70]

Health outcomes

Information on length of stay in hospital due to stroke, discharge destination and any readmissions to hospital were used to calculate the number of home time days per patient over a 12-month period. Home time has been previously used as an outcome measure in other stroke trials.[71,72] When data on actual discharge location were not available, the response to a question regarding place of residence at 3 months was used as a proxy for the discharge location. Discharge to institutional care (nursing home or residential care) was not counted as home time. The actual length of stay for readmissions was not available for all patients in the trial; therefore, a sample of 100 readmissions was analysed to determine the mean length of stay for a readmission. This value was attached to all patients who had a readmission, and used in the calculation of home time gained. Although the intention was to calculate home time gained in the first

90 days, as there were poor data on the date of readmission, home time gained was calculated over the full 12 months.

The EQ-5D-3L questionnaire[73] was completed at 3, 6 and 12 months, and when a patient had died during the 12 months, the date of death was noted and a value of zero (equivalent to dead) was assumed from the date of death. EQ-5D-3L data were not collected at baseline, as it was not possible for a patient admitted for a stroke to fill in a health-related quality of life questionnaire. Therefore, we used a previously published method[74] and assumed that the EQ-5D-3L score for all patients at baseline was zero, and the change in quality of life between baseline and 3 months was linear. An alternative method for baseline EQ-5D-3L score was used in a sensitivity analysis by assuming that the baseline quality of life was equal to the EQ-5D-3L value at 3 months. Quality of life estimates were derived from EQ-5D-3L responses provided by patients at each time point by applying the standard UK tariff values.[75] These estimates were then used to calculate total QALYs over 12 months for every individual in the study, using the area under the curve approach.

Resource use and costs

The costs included in the analysis related to oxygen administration as prescribed by the trial, additional oxygen required for other clinical reasons, length of stay in hospital, readmission to hospital and long-term care on discharge from hospital. All costs in the analysis were in UK pounds (£), based on a price year of 2013–14. Unit costs were obtained from published standard sources of costs for NHS procedures,[76] staff costs[77] and previously published research (*Table 2*). Health and Community Health Services pay and price indices were used to inflate costs, when appropriate.[77] Unit costs are listed in *Table 2*.

For the purposes of estimating the cost of oxygen administration as prescribed in the trial, it was assumed that, once a patient was allocated to a treatment arm, costs of treatment were incurred. The cost of oxygen administration was adjusted for those patients for whom continuous oxygen was prescribed for clinical reasons outside the trial treatment, as described in *Table 3*. Information on resources required for oxygen administration, including any additional staff time and equipment required for each treatment group, was collected prospectively during the trial using a short questionnaire filled in by a representative in 24 participating hospitals (see *Appendix 3*). The cost of each resource type was calculated in order to determine the cost of oxygen supplementation per trial arm (*Table 4*). All institutions included in the trial were assumed to have the same expertise and to have followed similar protocols in the management of patients.

Patients in the trial had a stroke, TIA or a stroke mimic. For a stroke, a NHS reference cost for a CVA was assumed, as the majority of strokes were ischaemic. As there were five different categories for CVA, taking into account the number of complications and comorbidities, the median was calculated for the cost of a non-elective long stay, cost of an excess bed-day and average length of stay. These values were then adjusted for the length of stay in hospital for each patient, either adding or subtracting a bed-day cost for length of stay under or over the median length of stay. For patients who had a TIA or stroke mimic, the NHS reference cost for a TIA was assumed, using the same methodology as for CVA to adjust for length of stay. As full data on the details and length of stay of any non-elective readmissions during the 12 months were not available, the overall average cost of a non-elective admission (for all categories) was used.

Patient-level resource use on long-term care beyond the initial hospital admission was unavailable; however, the responses to the mRS provided information on the level of dependence. Patients were categorised as independent (mRS score of 0–2) or dependent (mRS score of 3–5) using data from the 3-month questionnaire. The annual cost of independent and dependent stroke after discharge from hospital was obtained from Sandercock *et al.*[79] and updated to 2013/14 costs. This annual cost was then adjusted to take into account the time not in hospital over the 12-month period.

For the purpose of the analysis, the costs of acute stay in hospital and long-term care were not included in the cost-effectiveness analysis to avoid double counting, as the measure of outcome was home time gained.

TABLE 2 Health-care resource use unit costs

Health-care resource	Unit cost (£)	Source
Oxygen supplementation		
Staff costs (per hour)		
Sister/charge nurse	51	Curtis, 2014[77]
Registered nurse	34	
Student/research nurse	21	
Registrar	40	
Consultant	101	
Physiotherapist	33	
Allied professional	23	
Housekeeping	26	
Equipment cost (per item)		
Oxygen tubing	6.35	University Hospitals of North Midlands NHS Trust supplies document, 2015[78]
Portable oxygen cylinder	20.52	
Nasal tubes	4.85	
Oxygen mask	4.79	
Stroke inpatient stay		
Non-elective stay (10 days)	4171	*NHS Reference Costs 2013–14*[76]
Excess bed-day	275	
TIA/mimic inpatient stay		
Non-elective stay (4 days)	1775	*NHS Reference Costs 2013–14*[76]
Excess bed-day	235	
Readmission	2837	*NHS Reference Costs 2013–14*[76]
Long-term care[a]		
Stroke care after discharge for an independent patient (annual cost)	1412	Sandercock *et al.*, 2002[79]
Stroke care after discharge for a dependent patient	18,578	

a Stroke care after discharge includes ambulatory rehabilitation (use of therapists and residential facilities) and long-term care (nursing home, carer/sheltered home and own home).

TABLE 3 Assumptions made for adjusting the cost of oxygen supplementation for patients when continuous oxygen was prescribed for clinical reasons

No oxygen	Nocturnal oxygen	Continuous oxygen
Add 3 days of continuous oxygen	Add 1.5 days of continuous oxygen	Double the cost for the amount of oxygen given

TABLE 4 Costs of oxygen supplementation

Resource use and cost per patient (UK £, 2013/14)	Value (£)	Source
Nocturnal ROS		
Nurse[a]	23.6	SO_2S trial data (Curtis, 2014[77])
Allied professionals[b]	23.0	SO_2S trial data (Curtis, 2014[77])
Doctor[c]	1.9	SO_2S trial data (Curtis, 2014[77])
Physiotherapist	1.5	SO_2S trial data (Curtis, 2014[77])
Housekeeping	0.1	SO_2S trial data (Curtis, 2014[77])
Oxygen tubing	4.4	SO_2S trial data
Portable oxygen cylinder	2.7	SO_2S trial data
Nasal tubes	6.5	SO_2S trial data
Oxygen mask	0.6	SO_2S trial data
Total cost per patient	64.0	
Continuous ROS		
Nurse[a]	32.1	SO_2S trial data (Curtis, 2014[77])
Allied professionals[b]	29.0	SO_2S trial data (Curtis, 2014[77])
Doctor[c]	1.8	SO_2S trial data (Curtis, 2014[77])
Physiotherapist	2.2	SO_2S trial data (Curtis, 2014[77])
Housekeeping	0.1	SO_2S trial data (Curtis, 2014[77])
Oxygen tubing	4.4	SO_2S trial data
Portable oxygen cylinder	5.6	SO_2S trial data
Nasal tubes	6.7	SO_2S trial data
Oxygen mask	0.6	SO_2S trial data
Total cost per patient	83.0	

a Including sister/charge nurse, staff/registered nurse, nurse, registered nurse and student/research nurse.
b Including health care assistant or trainee allied professional.
c Including consultant/stroke physician and specialist registrar.

Analysis

The EQ-5D-3L and mRS data were not available for all randomised patients, and therefore, multiple imputation (MI) was used. MI is a statistical technique that retains overall population variability and the relationship between observations, and is considered useful when > 10% of data are missing. As > 10% of the data were missing within the trial, these were treated as missing at random and estimated using the Markov chain Monte Carlo MI method. Imputation of missing EQ-5D-3L scores used methods proposed by Simons *et al.*,[80] in which the whole index score was imputed. The percentage of missing EQ-5D-3L data at 12 months was 18%; therefore, 25 simulated, complete versions of the data set were produced using Stata 12.1 software (StataCorp LP, College Station, TX, USA). The results of each of the simulated data sets were combined to produce estimates and CIs to incorporate missing data uncertainty. MI was carried out at all time points. *Appendix 4* contains further detail on the imputation methods.

As the majority of cost and outcome data are usually skewed, normal parametric methods are not appropriate for calculation of the differences in means. Bootstrapping is a non-parametric approach that can be used to compare arithmetic means without making any assumptions regarding the sampling distribution. In this analysis, 3000 bootstrapping replications were undertaken in order to calculate the 95% CIs around the differences in mean costs and outcomes.

The incremental cost-effectiveness analysis was carried out at 12 months, based on the outcome of home time gained, and the incremental cost-effectiveness ratio (ICER) was expressed in terms of the cost per 1 additional day of home time gained at 12 months. A CUA was also carried out at 12 months and the ICERs were expressed as cost per additional QALY gained. The presentation of results in QALYs allows comparison of the results with other available published studies. The analysis was conducted according to the intention-to-treat principle, in line with the main trial analysis, and discounting was not applied as the duration of follow-up was only 1 year. First, an analysis of ROS compared with no ROS was conducted by including all patients in the nocturnal and continuous ROS arms in the overall ROS comparator. A subsequent analysis considered all three trial arms, using the principle of dominance: that is, if one of the trial arms was shown to be both more costly and less effective than at least one of the alternative interventions, then that option would be seen as dominated and excluded from remainder of the analysis.

A range of one-way deterministic sensitivity analyses were carried out to explore the robustness of the base-case cost–utility results for ROS compared with no ROS, and to assess the uncertainty associated with input parameters. The following sensitivity analyses were undertaken:

- changing the costs of oxygen treatment (increasing/reducing the costs by 20%)
- changing the acute inpatient costs of stroke (reducing/increasing the costs by 20%)
- changing the costs of stroke care after discharge (reducing/increasing the costs by 20%)
- assuming that quality of life changes between base-case and 3 months took place immediately, therefore allocating the 3 month EQ-5D-3L value to baseline.

In addition, a probabilistic sensitivity analysis of the base-case analysis (cost-effectiveness analysis and CUA) was carried out to enable the simultaneous exploration of uncertainty in the cost and outcome data, using 5000 simulations. The results of the probabilistic sensitivity analysis are presented using cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs). The CEAC graphically represents the probability that an intervention is cost-effective at different ICER thresholds.

All analyses were carried out using Stata version 12.1 and Microsoft Excel® 2007 (Microsoft Corporation, Redmond, WA, USA).

Patient and public involvement

We conducted focus group meetings with stroke survivors when preparing the protocol for SO_2S (see Ali *et al.*[46] for detail). Stroke survivors and their carers considered the study important. They considered the outcomes relevant, but suggested others that were not adequately covered by the formal assessment tools. These included memory, speech problems and sleep. We designed questions to specifically address these points and included them in the assessments at 3, 6 and 12 months. We also discussed consent issues, as many stroke patients are unable to give fully informed consent soon after the stroke, because of the nature of their brain injury. Some of the stroke patients were concerned that asking relatives to provide consent on behalf of the patients would put them under too much stress at a time when they were anxious and worried. We explained that there was an option of allowing an independent physician to consent on behalf of the patient. We included patient and carer representatives as collaborators and as members of the trial management group. Over the time of the study the initial collaborators (Linda and Peter Handy) became unable to contribute further for health reasons. Towards the end of the study Norman Phillips and Brin Helliwell provided advice to the trial management group and input into the report.

Ethical approval

The protocol was approved by the North Staffordshire Ethics Committee (06/2604/109) on 24 January 2007. The protocol can be accessed at http://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-15-99 (accessed 1 June 2016).

Clinical trials registration

European Union Drug Regulating Authorities Clinical Trials (EudraCT) number 2006-003479-11 and Current Controlled Trials International Standard Randomised Controlled Trial Number (ISRCTN) 52416964.

Chapter 3 Results

Recruitment

In total 8003 patients were recruited between 24 April 2008 and 17 June 2013 (*Figure 2*). Participants were randomised to the three groups: 2668 to the control group, 2668 to the continuous oxygen group and 2667 to the nocturnal oxygen group. All follow-up assessments were completed by December 2014.

Consent and patient flow through the study

Fully informed consent was given by 6991 (87%) of patients and assent was given by a relative, carer or independent legal representative for 1012 (13%) patients (*Table 5*). At the 7-day review, six (0.7%) assented patients refused consent and were withdrawn from the study. A further 22 assented patients were withdrawn between days 7 and 90, six between days 90 and 180, and two between day 180 and the end of the study. Of those patients who gave informed consent, 40 were withdrawn by day 7, 114 were withdrawn from the study between day 7 and day 90 post randomisation, 37 were withdrawn between day 90 and 180, and 30 withdrew between days 180 and 365 (*Figure 3*).

Baseline data

Patient age and sex distribution were similar in all three groups. Overall mean age was 72 years (SD 13 years) and in total 4398 (55%) patients were male. Prognostic factors, including independence in activities of daily living before the stroke ($n = 7332$, 92%), were also well matched across the trial arms. There was little to no difference in the participants' medical history, with ischaemic heart disease ($n = 1602$, 20%), heart failure ($n = 657$, 8%), atrial fibrillation ($n = 1995$, 25%) and chronic lung conditions ($n = 812$, 10%) recorded in each group. Patients were enrolled relatively late at a median 20:43 (IQR 11:59–25:32) hours:minutes after symptom onset. The majority of patients had a final diagnosis of ischaemic stroke ($n = 6555$, 82%) recorded at the 7-day review. Primary intracerebral haemorrhage was diagnosed in 588 (7%) patients, TIA in 168 (2%) and non-stroke conditions in 292 (4%); this information was missing for 106 patients (1%). The median GCS score was 15 (IQR 15–15) and mean and median NIHSS scores were 7 and 5, respectively (range 0–34); again these were well balanced across the trial arms. Twenty per cent of patients received oxygen prior to randomisation and the mean oxygen saturation was 96.6% in the continuous (SD 1.7) and nocturnal oxygen (SD 1.6) treatment groups, and 96.7% (SD 1.7) in the control group (*Table 6*).

Treatment adherence

Treatment adherence in the two intervention arms was similar, with 2158 (81%) patients completing the 72 hours of continuous oxygen therapy and 2225 (83%) patients receiving the nocturnal oxygen. In the continuous group, 433 (16%) patients did not receive the full 72 hours of oxygen therapy, and in the nocturnal group 361 (14%) did not. Discharge from hospital was the main reason for stopping before the 72 hours had passed (*Table 7*). In the control group trial oxygen was not prescribed for 2229 (84%) participants, but was prescribed for 23 (1%) participants; this information was not available for 406 (15%) control participants.

In a subgroup of 4144 patients spot checks of adherence to oxygen treatment were made at 00:00 and 06:00 on nights 1, 2, and 3 of the intervention (*Table 8*). On the first night, adherence to oxygen treatment was reasonable, with oxygen in place for 82% and 78% for the continuous and nocturnal oxygen groups, respectively, at midnight and in 82% and 72%, respectively, at 06:00. During nights 2 and 3, considerably fewer spot checks were recorded as positive, with the lowest being 56% and 51% for the continuous and nocturnal oxygen groups at 06:00 of night 3. In the control group, oxygen

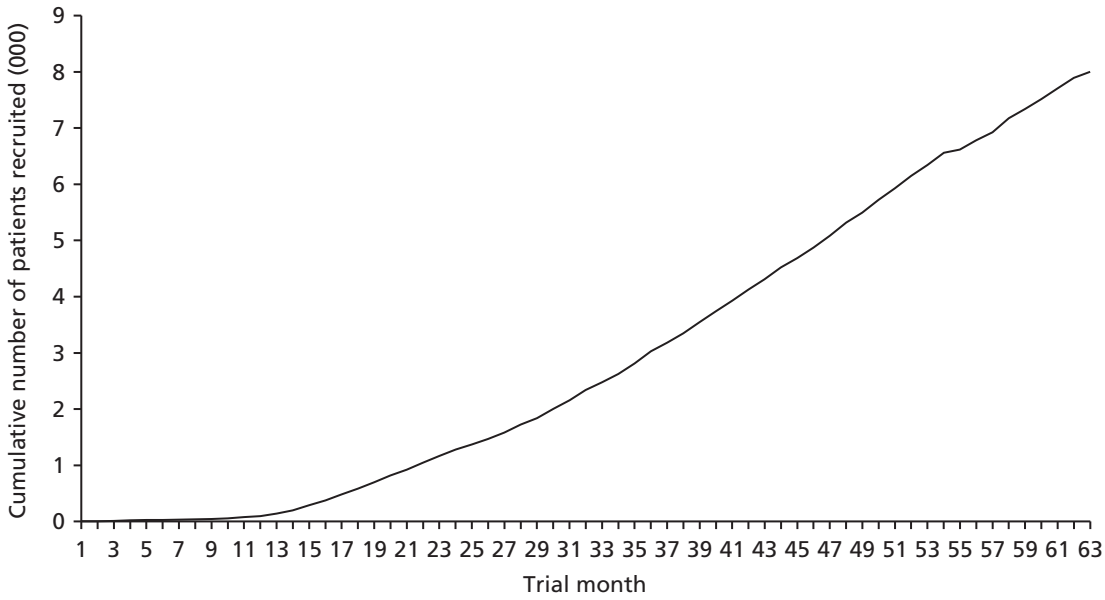

FIGURE 2 Timeline of patients recruited to SO_2S over a 5-year period.

TABLE 5 Cumulative withdrawal data for SO_2S study at each of the follow-up time points

Variable	Trial arm		
	Continuous oxygen ($N = 2668$)	Nocturnal oxygen ($N = 2667$)	Control ($N = 2668$)
Consent given by the patient, *n* (%)	2329 (87)	2340 (88)	2322 (87)
Consent given by a relative, carer or independent legal representative, *n* (%)	339 (13)	327 (12)	346 (13)
Withdrawal from trial by 7 days,* n *(%)			
Total	16 (0.6)	20 (0.7)	4 (0.15)
Patients who gave initial consent themselves	14 (0.5)	17 (0.6)	3 (0.11)
Patients included by a legal representative	2 (0.1)	3 (0.1)	1 (0.04)
Withdrawal from trial by 90 days,* n *(%)			
Total	56 (2.1)	63 (2.4)	57 (2.1)
Patients who gave initial consent themselves	48 (1.8)	56 (2.1)	44 (1.6)
Patients included by a legal representative	8 (0.3)	7 (0.3)	13 (0.5)
Withdrawal from trial by 180 days,* n *(%)			
Total	77 (2.9)	72 (2.7)	70 (2.6)
Patients who gave initial consent themselves	67 (2.5)	63 (2.4)	55 (2.1)
Patients included by a legal representative	10 (0.4)	9 (0.3)	15 (0.6)
Withdrawal from trial by 365 days,* n *(%)			
Total	89 (3.3)	81 (3.0)	81 (3.0)
Patients who gave initial consent themselves	78 (2.9)	71 (2.7)	66 (2.5)
Patients included by a legal representative	11 (0.4)	10 (0.4)	15 (0.6)

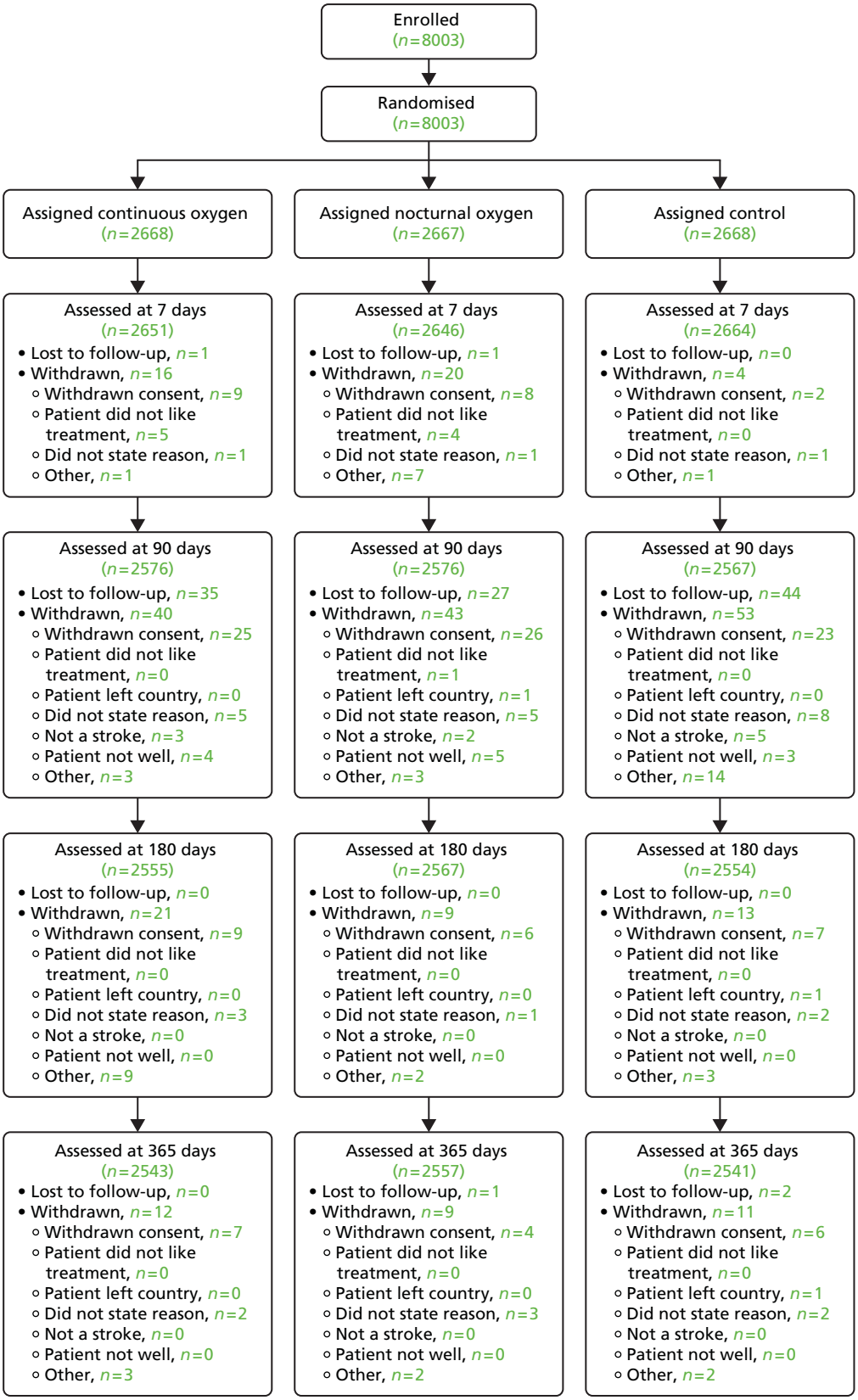

FIGURE 3 Consolidated Standards of Reporting Trials (CONSORT) flow chart for SO_2S.

TABLE 6 Baseline characteristics of patients recruited to SO_2S

Variable	Trial arm		
	Continuous oxygen (*N* = 2668)	Nocturnal oxygen (*N* = 2667)	Control (*N* = 2668)
Demographic characteristics			
Age (years)			
Mean (SD)[a]	72 (13)	72 (13)	72 (13)
Median (IQR)	74 (64–82)	75 (65–82)	74 (64–82)
Male sex; *n* (%)[a]	1466 (55)	1466 (55)	1466 (55)
Prognostic factors			
Living alone, *n* (%)[a]	861 (32)	857 (32)	907 (34)
Independent in basic activities of daily living, *n* (%)[a]	2451 (92)	2431 (91)	2450 (92)
Normal verbal response, *n* (%)[a]	2190 (82)	2207 (83)	2196 (82)
Able to lift affected arm, *n* (%)[a]	1998 (75)	2022 (76)	1996 (75)
Able to walk, *n* (%)[a]	660 (25)	704 (26)	677 (25)
Probability of 30-day survival, median (IQR)	0.92 (0.86–0.95)	0.92 (0.86–0.95)	0.92 (0.86–0.95)
Probability of being alive and independent at 6 months, median (IQR)[a]	0.44 (0.12–0.71)	0.42 (0.12–0.71)	0.42 (0.12–0.71)
Blood glucose (mmol/l), mean (SD)	7.1 (2.5)	7.0 (2.4)	7.1 (2.5)
Concomitant medical problems			
Ischaemic heart disease, *n* (%)	573 (21)	515 (19)	514 (19)
Heart failure, *n* (%)	224 (8)	217 (8)	216 (8)
Atrial fibrillation, *n* (%)	638 (24)	673 (25)	684 (26)
Chronic obstructive pulmonary disease/asthma, *n* (%)	253 (9)	242 (9)	245 (9)
Other chronic lung problem, *n* (%)	29 (1)	24 (1)	19 (1)
Details of the qualifying event			
Time since symptom onset (hh:mm), mean (IQR)[b]	20:44 (11:53–25:33)	20:32 (12:05–25:31)	20:45 (11:57–25:31)
Ischaemic stroke, *n* (%)[b]	2187 (82.0)	2165 (81.1)	2203 (82.6)
Intracranial haemorrhage, *n* (%)[b]	185 (6.9)	207 (7.8)	196 (7.3)
TIA, *n* (%)[b]	52 (1.9)	50 (1.9)	66 (2.5)
Stroke without imaging diagnosis, *n* (%)[b]	104 (3.9)	106 (4.0)	84 (3.1)
Not a stroke, *n* (%)[b]	101 (3.8)	98 (3.7)	93 (3.5)
Missing, *n* (%)[b]	39 (1.5)	41 (1.5)	26 (1.0)
GCS score (3–15), median (IQR)	15 (15–15)	15 (15–15)	15 (15–15)
Thrombolysed, *n* (%)[b]	447 (17)	410 (15)	447 (17)
NIHSS score (0–42), median (IQR)	5 (3–9)	5 (3–9)	5 (3–9)
Oxygenation			
Oxygen given prior to randomisation (yes), *n* (%)[a]	531 (20)	531 (20)	539 (20)
Oxygen saturation on room air (%), mean (SD)[a]	96.6 (1.7)	96.6 (1.6)	96.7 (1.7)

a Minimisation variables.
b Data were recorded on day 7.
Data in this table were collected before randomisation unless marked as otherwise.

TABLE 7 Adherence to trial treatment

Variable	Trial arm		
	Continuous oxygen (*N* = 2668)	Nocturnal oxygen (*N* = 2667)	Control (*N* = 2668)
Trial oxygen prescribed in the drug chart and signed, *n* (%)	1369 (51.3)	1426 (53.5)	21 (0.8)
Trial oxygen prescribed in the drug chart but not signed, *n* (%)	789 (29.6)	799 (30)	2 (0.1)
Trial oxygen stopped before 72 hours, *n* (%)	433 (16.2)	361 (13.5)	10 (0.4)
No oxygen prescribed for the trial as per randomisation, *n* (%)	4 (0.2)	10 (0.4)	2229 (83.5)
No data, *n* (%)	73 (2.7)	71 (2.6)	406 (15.2)

TABLE 8 Spot checks of adherence to the trial intervention in a subgroup of 4144 patients

Variable	Trial arm		
	Continuous oxygen (*N* = 1381)	Nocturnal oxygen (*N* = 1381)	Control (*N* = 1382)
Staff checked and signed that oxygen is in place at midnight			
Night 1, *n* (%)	1134 (82)	1074 (78)	31 (2)
Night 2, *n* (%)	970 (70)	931 (67)	38 (3)
Night 3, *n* (%)	803 (58)	772 (56)	37 (3)
Staff checked and signed that oxygen is in place at 6 am			
Night 1, *n* (%)	1132 (82)	994 (72)	37 (3)
Night 2, *n* (%)	954 (69)	863 (62)	45 (3)
Night 3, *n* (%)	774 (56)	703 (51)	39 (3)

was recorded as being in place at 00:00 in 2%, 3%, and 3% at 00:00 on nights 1, 2, and 3, respectively, and in 3% at 06:00 for each of the 3 days. The percentages are for a total of all patients randomised after the protocol change and included patients who were no longer in hospital.

Primary outcome

The distribution of scores for mRS at 90 days is shown in *Figure 4*. Oxygen supplementation did not improve the level of disability either in the comparison of the combined oxygen group against control or in the comparison of continuous versus nocturnal oxygen, both in the primary unadjusted analysis and in the covariate-adjusted analysis. The unadjusted OR for a better outcome (lower mRS) was 0.97 (95% CI 0.89 to 1.05; $p = 0.5$) for combined oxygen versus control (see *Figure 4a*), and 1.03 (95% CI 0.93 to 1.13; $p = 0.6$) for continuous oxygen versus nocturnal oxygen (see *Figure 4b*). Analyses adjusted for the covariates age, sex, baseline NIHSS score, baseline oxygen saturation and the SSV prognostic index yielded very similar results [an OR of 0.97 (95% CI 0.89 to 1.06; $p = 0.5$) for the combined oxygen group vs. control and an OR of 1.01 (95% CI 0.92 to 1.12; $p = 0.8$) for continuous oxygen vs. oxygen at night only].

The primary outcome of the SO_2S was the mRS score at 90 days post stroke as a measure of disability and dependence: (1) comparing the control group (no oxygen supplementation) with both the continuous (72 hours, day and night) and nocturnal (for three nights only) groups combined; and (2) comparing continuous oxygen with nocturnal oxygen.

Sensitivity analyses for the primary outcome

Sensitivity analyses (*Table 9*) show very similar results for the complete case analysis and the analysis using MI for missing values, both confirming that oxygen treatment does not improve the primary outcome. The best- and worst-case imputations indicate the plausible maximum bounds of any potential bias from

(a)

		mRs	0	1	2	3	4	5	6
Control	*n*		336	671	330	415	395	156	246
	Percentage		13	26	13	16	16	6	10

		mRs	0	1	2	3	4	5	6
Combined oxygen	*n*		605	1399	637	883	795	316	493
	Percentage		12	27	12	17	16	6	10

(b)

		mRs	0	1	2	3	4	5	6
Continuous oxygen	*n*		313	690	322	461	376	148	257
	Percentage		12	27	12	18	15	6	10

		mRs	0	1	2	3	4	5	6
Nocturnal oxygen	*n*		292	709	315	422	419	168	236
	Percentage		11	28	12	17	16	7	9

FIGURE 4 The primary outcome: mRS at 3 months. (a) Comparison 1 (combined oxygen vs. control); and (b) comparison 2 (continuous oxygen vs. nocturnal oxygen). Adapted with permission from Roffe *et al.*[81]

TABLE 9 Sensitivity analyses

Variable	OR (95% CI); *p*-value	
	Oxygen vs. no oxygen[a]	Continuous vs. nocturnal[b]
Complete case analysis	0.970 (0.892 to 1.054); 0.471	1.025 (0.931 to 1.129); 0.611
MI analysis[c]	0.974 (0.895 to 1.061); 0.549	1.031 (0.933 to 1.135); 0.530
Best-case imputation[d]	1.178 (1.085 to 1.279); < 0.001	1.221 (1.111 to 1.342); < 0.001
Worst-case imputation[e]	0.803 (0.740 to 0.872); < 0.001	0.862 (0.784 to 0.947); 0.002
Adherers only[f]	0.925 (0.833 to 1.028); 0.148	0.981 (0.853 to 1.127); 0.782

Analyses are unadjusted unless specified otherwise.
a Reference category is 'no oxygen'; outcome is a 1-point lower (better) score on mRS.
b Reference category is 'nocturnal'; outcome is a 1-point lower (better) score on mRS.
c Based on 20 imputed data sets.
d Missing values for 'oxygen' and 'continuous' are given a good score (0 or 1), missing cases for 'no oxygen' and 'nocturnal' are given a poor score (5 or 6); CIs and *p*-values have been adjusted for the imputation.
e Missing values for 'oxygen' and 'continuous' are given a poor score (5 or 6), missing cases for 'no oxygen' and 'nocturnal' are given a good score (0 or 1); CIs and p-values have been adjusted for the imputation.
f Trial oxygen prescribed and signed as given: control, $n = 1994$; continuous Oxygen, $n = 1285$; nocturnal Oxygen, $n = 1250$; combined Oxygen, $n = 2535$. Analysis adjusted for age, sex, baseline NIHSS score, baseline oxygen saturation, and SSV prognostic index for 6-month independence, to account for loss of equivalence from randomisation.

missing data (under a missing not at random assumption), showing improvement in outcome for oxygen for the best-case analysis and worse outcomes with oxygen for the worst-case analysis, with similar effect sizes in both directions. The adherers-only analyses showed a minor difference between the combined oxygen groups and control, with slightly lower odds for a good outcome with oxygen for the comparison of the combined oxygen groups with control, which was not statistically significant.

Subgroup analyses

The predefined subgroup analyses are shown in *Figure 5*. There was no indication that treatment effectiveness differed for any of the predefined subgroups (oxygen treatment before enrolment, oxygen

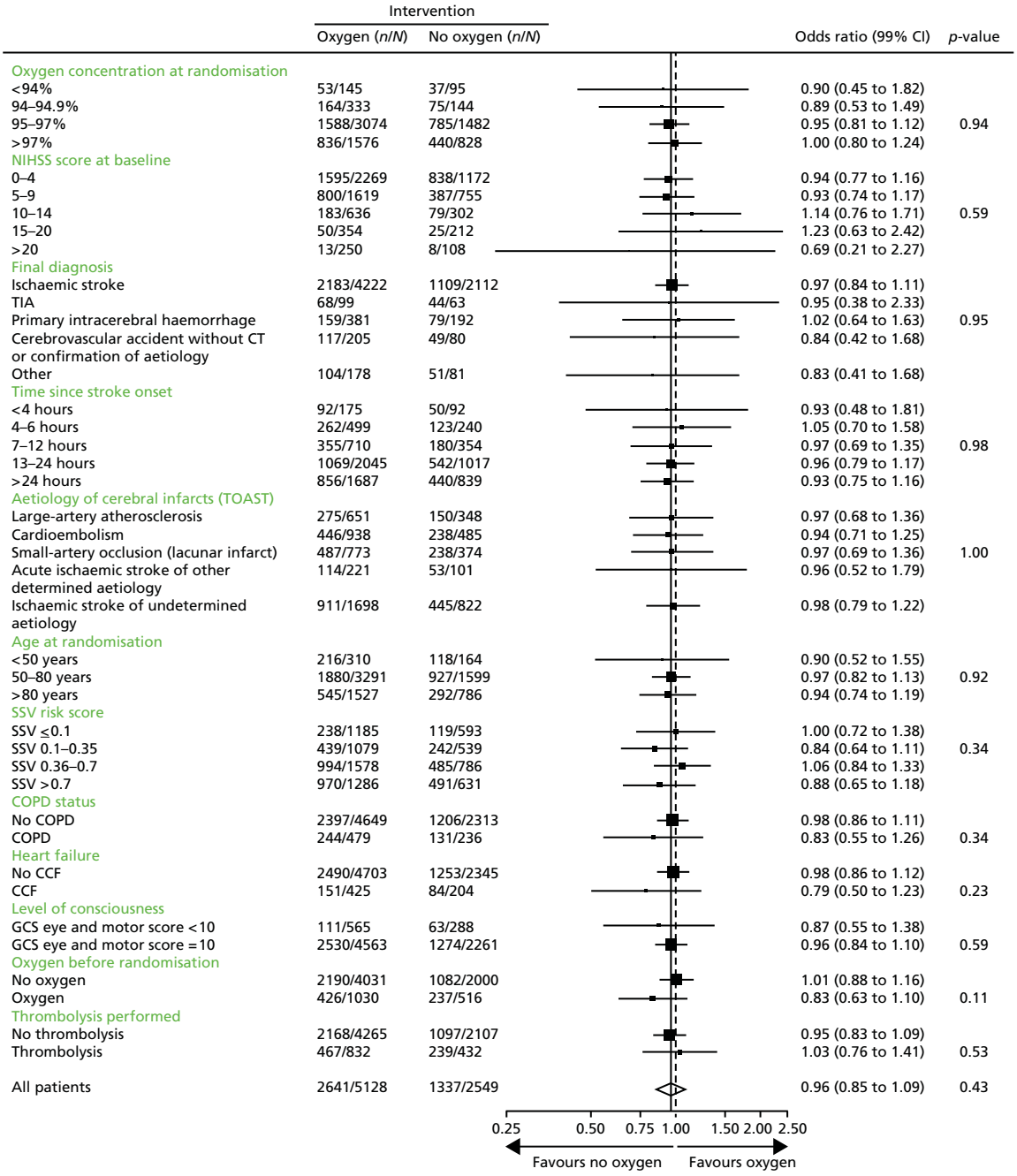

FIGURE 5 Forest plot of subgroup analyses: alive and independent (mRS score of ≤ 2) at 3 months of oxygen (continuous and nocturnal combined) compared with control. *n* is the total number of events and *N* is the total number of events plus non-events for that group. COPD, chronic obstructive pulmonary disease; CCF, congestive cardiac failure.

saturation on air at randomisation, NIHSS score, final diagnosis, time since stroke onset, aetiology, age, SSV prognostic index, level of consciousness, and history of heart failure or of chronic obstructive airways disease).

Secondary and explanatory outcomes at 1 week

Oxygenation

Results for the highest oxygen saturation, the lowest oxygen saturation, the number of patients who had desaturations below 90% and the number of patients who needed additional oxygen over and above the trial prescription during the first 72 hours are shown in *Table 10*. The highest and lowest oxygen saturations recorded during the treatment period increased significantly ($p < 0.001$), by 0.8% and 0.9% respectively, in the continuous oxygen group when compared with the control group. This was also seen in the nocturnal oxygen group with highest and lowest oxygen saturations increased by 0.5% and 0.4%, respectively ($p < 0.001$). Severe hypoxia was recorded in a small number of patients (143, 2%), but was significantly less common in the combined oxygen group than in the control group. Significantly more patients in the combined oxygen group than in the control group required oxygen in addition to the trial intervention (OR 1.36, 99% CI 1.07 to 1.73; $p = 0.0008$). This was also not statistically different when comparing continuous with nocturnal oxygen (OR 1.23, 99% CI 0.96 to 1.59; $p = 0.03$), as significance was defined as < 0.01 for secondary outcomes.

Neurological recovery at 1 week

Data for neurological recovery and mortality at 1 week are shown in *Table 11*. The median (IQR) NIHSS score at week 1 was 2 (1–6) in all three treatment groups. There was no difference in the number of patients who improved by 4 or more NIHSS points between baseline and week 1. Mortality by day 7 was very low in all three treatment groups with 50 (1.9%), 35 (1.3%) and 45 (1.7%) deaths in the continuous oxygen, nocturnal oxygen and control groups, respectively.

Explanatory analysis at 1 week

Exploratory analyses (see *Table 11*) did not show evidence of increased stress levels (higher heart rates, higher blood pressure, or need for sedation) in oxygen-treated patients compared with control patients. There was also no evidence that oxygen treatment was associated with more infections, with no differences in the highest temperature or the need for antibiotics.

Secondary and exploratory outcomes at 3 months

There was no difference in mortality, the number of patients alive and independent at 3 months, the number of participants who lived at home, the BI, the NEADL, EQ-5D-3L, EQ-VAS, sleep, speech or memory between the oxygen-treated and control groups or between the groups receiving continuous and nocturnal oxygen treatment (*Table 12*).

Long-term outcomes (3, 6 and 12 months)

Survival

Mortality at 90 days (*Figure 6*) was similar in the oxygen (both groups combined) and control groups (hazard ratio 0.97, 99% CI 0.78 to 1.21; $p = 0.8$) and in the groups recieving continuous oxygen or oxygen at night only (hazard ratio 1.15, 99% CI 0.90–1.48; $p = 0.1$).

Survival was the same throughout the 365 days of follow-up for patients treated with continuous oxygen and with nocturnal oxygen, and those in the control group (*Figure 7*).

TABLE 10 Oxygenation-related secondary outcomes

Variable	*n* (*N* = 8003)	Trial arm			Oxygen vs. control, OR or MD (99% CI)	Oxygen vs. control, *p*-value	Continuous vs. nocturnal, OR or MD (99% CI)	Continuous vs. nocturnal, *p*-value
		Continuous oxygen (*n* = 2668)	Nocturnal oxygen (*n* = 2667)	Control (*n* = 2668)				
Highest oxygen saturation (%)[a]	7860	99.1 (99.1 to 99.2), *n* = 2620	98.8 (98.7 to 98.9), *n* = 2609	98. 3 (98.2 to 98.3), *n* = 2631	0.69 (0.61 to 0.77)	< 0.0001[c]	0.32 (0.22 to 0.41)	< 0.0001[c]
Lowest oxygen saturation (%)[a]	7860	95.0 (94.9 to 95.1), *n* = 2619	94.5 (94.4 to 94.6), *n* = 2610	94.1 (94.0 to 94.2), *n* = 2631	0.62 (0.48 to 0.76)	< 0.0001[c]	0.48 (0.32 to 0.63)	< 0.0001[c]
Oxygen saturation < 90%[b]	7860	39 (1.5%), *n* = 2619	30 (1.1%), *n* = 2610	74 (2.8%), *n* = 2631	0.46 (0.30 to 0.71)	< 0.0001[d]	1.30 (0.69 to 2.44)	0.27[d]
Need for additional oxygen[b]	7809	254 (9.8%), *n* = 2599	209 (8.1%), *n* = 2589	176 (6.7%), *n* = 2621	1.36 (1.07 to 1.73)	0.0008[d]	1.23 (0.96 to 1.59)	0.03[d]

MD, mean difference.
a Data are given as means and 95% CIs.
b Data are given as numbers and percentages.
c Significance testing was by unrelated *t*-test.
d Significance testing was by chi-squared test.
MDs are reported for means, and ORs for frequencies.

TABLE 11 Secondary and exploratory outcomes at 1 week

Variable	*n* (*N* = 8003)	Trial arm			Oxygen vs. control, OR or MD (99% CI)	Oxygen vs. control, *p*-value	Continuous vs. nocturnal, OR or MD (99% CI)	Continuous vs. nocturnal, *p*-value
		Continuous oxygen (*n* = 2668)	Nocturnal oxygen (*n* = 2667)	Control (*n* = 2668)				
Neurological improvement, *n* (%)	7778	1016 (39.2%), *n* = 2591	1029 (39.7%), *n* = 2591	1037 (39.9%), *n* = 2596	0.98 (0.86 to 1.11)	0.68[a]	0.98 (0.85 to 1.13)	0.71[a]
NIHSS, median (IQR)	7778	2 (1–6), *n* = 2591	2 (1–6), *n* = 2591	2 (1–6), *n* = 2596	–0.04 (–0.43 to 0.34)	0.78[b]	0.12 (–0.32 to 0.57)	0.47[b]
Death by 7 days, *n* (%)	7959	50 (1.9%), *n* = 2651	35 (1.3%), *n* = 2645	45 (1.7%), *n* = 2663	0.95 (0.59 to 1.53)	0.78[a]	1.43 (0.81 to 2.54)	0.11[a]
Highest heart rate (b.p.m.), mean (SD)	7859	87.2 (16.6), *n* = 2618	88.0 (16.5), *n* = 2609	87.7 (15.7), *n* = 2632	–0.07 (–1.06 to 0.92)	n/a	–0.83 (–2.01 to 0.35)	n/a
Highest systolic blood pressure (mmHg), mean (SD)	7864	162.4 (24.6), *n* = 2621	162.8 (24.8), *n* = 2610	164.6 (24.7), *n* = 2633	–1.96 (–3.48 to 0.44)	n/a	–0.35 (–2.11 to 1.41)	n/a
Highest diastolic blood pressure (mmHg), mean (SD)	7861	89.5 (15.3), *n* = 2621	90.2 (15.5), *n* = 2609	90.9 (15.7), *n* = 2631	–1.10 (–2.06 to 0.15)	n/a	–0.72 (–1.82 to 0.37)	n/a
Highest systolic blood pressure > 200 mmHg (*n*)	7864	180, *n* = 2621	186, *n* = 2610	205, *n* = 2633	n/a	n/a	n/a	n/a
Highest diastolic blood pressure > 100 mmHg (*n*)	7861	531, *n* = 2621	552, *n* = 2609	606, *n* = 2631	n/a	n/a	n/a	n/a
Sedative use, *n* (%)	7916	140 (5.3%), *n* = 2634	161 (6.1%), *n* = 2631	154 (5.8%), *n* = 2651	0.98 (0.76 to 1.28)	n/a	0.86 (0.63 to 1.17)	n/a
Antibiotic treatment, *n* (%)	7916	400 (15.2%), *n* = 2634	393 (14.9%), *n* = 2631	403 (15.2%), *n* = 2651	0.99 (0.83 to 1.17)	n/a	1.02 (0.84 to 1.24)	n/a
Highest temperature (°C) up to 7 days, mean (SD)	7877	37.1 (0.6), *n* = 2623	37.2 (0.6), *n* = 2617	37.1 (0.6), *n* = 2637	0.01 (–0.03 to 0.04)	n/a	–0.01 (–0.05 to 0.03)	n/a

b.p.m., beats per minute; MD, mean difference; n/a, not applicable.
a Significance testing was by chi-squared test.
b Significance testing was by unrelated *t*-test.
Secondary outcomes were neurological improvement, and mortality 7 days post randomisation. Blood pressure and heart rate during the first 72 hours and temperature, sedative use, and antibiotic treatment up to day 7 were exploratory outcomes. Exploratory outcomes were not analysed statistically. Neurological improvement was defined as a ≥ 4-point decrease from baseline or a value of 0 for NIHSS at 7 days.

TABLE 12 Secondary and exploratory outcomes at 3 months

Variable	*n* (*N* = 8003)	Trial arm			Oxygen vs. control, OR or MD (99% CI)	Oxygen vs. control, *p*-value	Continuous vs. nocturnal, OR or MD (99% CI)	Continuous vs. nocturnal, *p*-value
		Continuous oxygen (*n* = 2668)	Nocturnal oxygen (*n* = 2667)	Control (*n* = 2668)				
Death by 3 months	7677	257 (10.0%), *n* = 2567	236 (9.2%), *n* = 2561	246 (9.7%), *n* = 2549	1.00 (0.81 to 1.23)	0.96[b]	1.10 (0.86 to 1.40)	0.33[b]
Death by 90 days[a] (date)	8003	222 (8.3%), *n* = 2668	194 (7.3%), *n* = 2667	214 (8.0%), *n* = 2668	0.97 (0.77 to 1.22)	0.73[b]	1.16 (0.89 to 1.51)	0.15[b]
Alive and independent[a]	7677	1325 (51.6%), *n* = 2567	1316 (51.4%), *n* = 2561	1337 (52.5%), *n* = 2549	0.96 (0.85 to 1.09)	0.43[b]	1.01 (0.87 to 1.17)	0.87[b]
Living at home[a]	6859	1961 (85.8%), *n* = 2285	1947 (84.8%), *n* = 2295	1947 (85.4%), *n* = 2279	0.99 (0.82 to 1.20)	0.91[b]	1.08 (0.87 to 1.34)	0.35[b]
Barthel ADL index [0 (worst) to 100 (best)][c]	6549	70.2 (68.7 to 71.8), *n* = 2169	71.1 (69.6 to 72.6), *n* = 2194	70.9 (69.3 to 72.4), *n* = 2186	–0.18 (–2.60 to 2.24)	0.85[d]	–0.86 (–3.65 to 1.93)	0.43[d]
Nottingham Extended ADL [0 (worst) to 21 (best)][c]	7528	9.66 (9.38 to 9.93), *n* = 2520	9.54 (9.26 to 9.81), *n* = 2501	9.77 (9.49 to 10.05), *n* = 2507	–0.17 (–0.62 to 0.28)	0.32[d]	0.12 (–0.40 to 0.64)	0.55[d]
Quality of life (EQ-5D-3L) [–0.59 (worst) to 1 (best)][c]	7248	0.50 (0.48 to 0.51), *n* = 2413	0.50 (0.48 to 0.51), *n* = 2428	0.49 (0.48 to 0.51), *n* = 2407	0.004 (0.02 to 0.03)	0.71[d]	–0.003 (–0.03 to 0.03)	0.78[d]
Quality of life (EQ-VAS) [0 (worst) to 100 (best)][c]	6675	55.4 (54.2 to 56.7), *n* = 2251	55.7 (54.4 to 56.9), *n* = 2216	55.5 (54.2 to 56.7), *n* = 2208	0.10 (–1.93 to 2.12)	0.90[d]	–0.24 (–2.57 to 2.09)	0.79[d]

continued

TABLE 12 Secondary and exploratory outcomes at 3 months (*continued*)

Variable	*n* (*N* = 8003)	Trial arm			Oxygen vs. control, OR or MD (99% CI)	Oxygen vs. control, *p*-value	Continuous vs. nocturnal, OR or MD (99% CI)	Continuous vs. nocturnal, *p*-value
		Continuous oxygen (*n* = 2668)	Nocturnal oxygen (*n* = 2667)	Control (*n* = 2668)				
Sleep as good as before the stroke[a]	6584	1407 (64%), *n* = 2194	1436 (65%), *n* = 2208	1419 (65%), *n* = 2182	0.98 (0.85 to 1.13)	–	0.96 (0.82 to 1.13)	–
No significant speech problems[a]	6716	1957 (88%), *n* = 2229	1957 (87%), *n* = 2246	1939 (87%), *n* = 2241	1.09 (0.89 to 1.32)	–	1.06 (0.84 to 1.34)	–
Memory as good as before the stroke[a]	6646	981 (44%), *n* = 2222	1000 (45%), *n* = 2224	971 (44%), *n* = 2200	1.02 (0.89 to 1.16)	–	0.97 (0.83 to 1.13)	–

ADL, activities of daily living; EQ-5D-3L, European Quality of Life-5 DImensions, three levels; MD, mean difference.
a Data are given as numbers and percentages.
b Significance testing was by chi-squared test.
c Data are given as means and 99% CIs.
d Significance testing was by unrelated *t*-test.
MDs are reported for means, and ORs for numbers. Alive and independent is a mRS score of two or fewer. As outlined in the statistical analysis plan, we have not conducted significance tests on the exploratory data and the outcomes suggested by patients and carers.

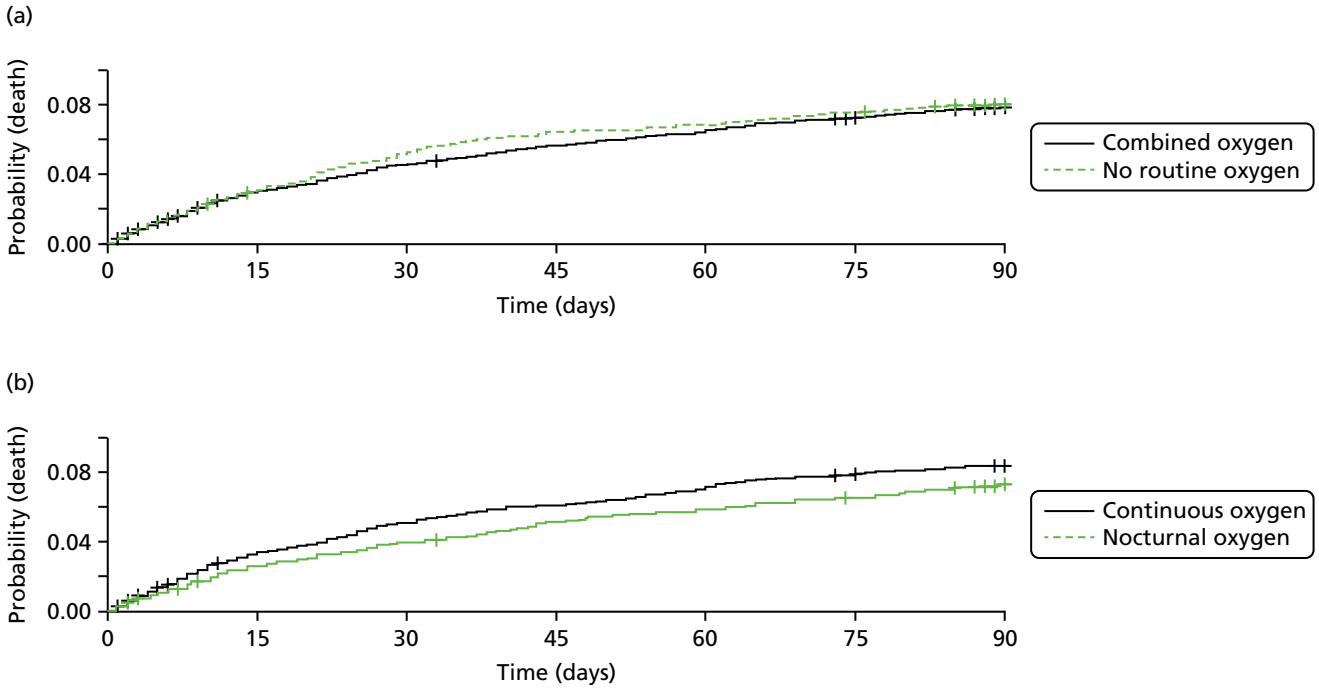

FIGURE 6 Kaplan–Meier survival graph comparing (a) oxygen (combined) with control (no ROS) at 90 days; and (b) continuous vs. nocturnal oxygen. Oxygen compared with no oxygen: unadjusted hazard ratio for a worse outcome – 0.97 (99% CI 0.78 to 1.21; $p = 0.8$). Continuous compared with nocturnal oxygen: unadjusted hazard ratio for a worse outcome –1.15 (99% CI 0.90 to 1.48; $p = 0.1$).

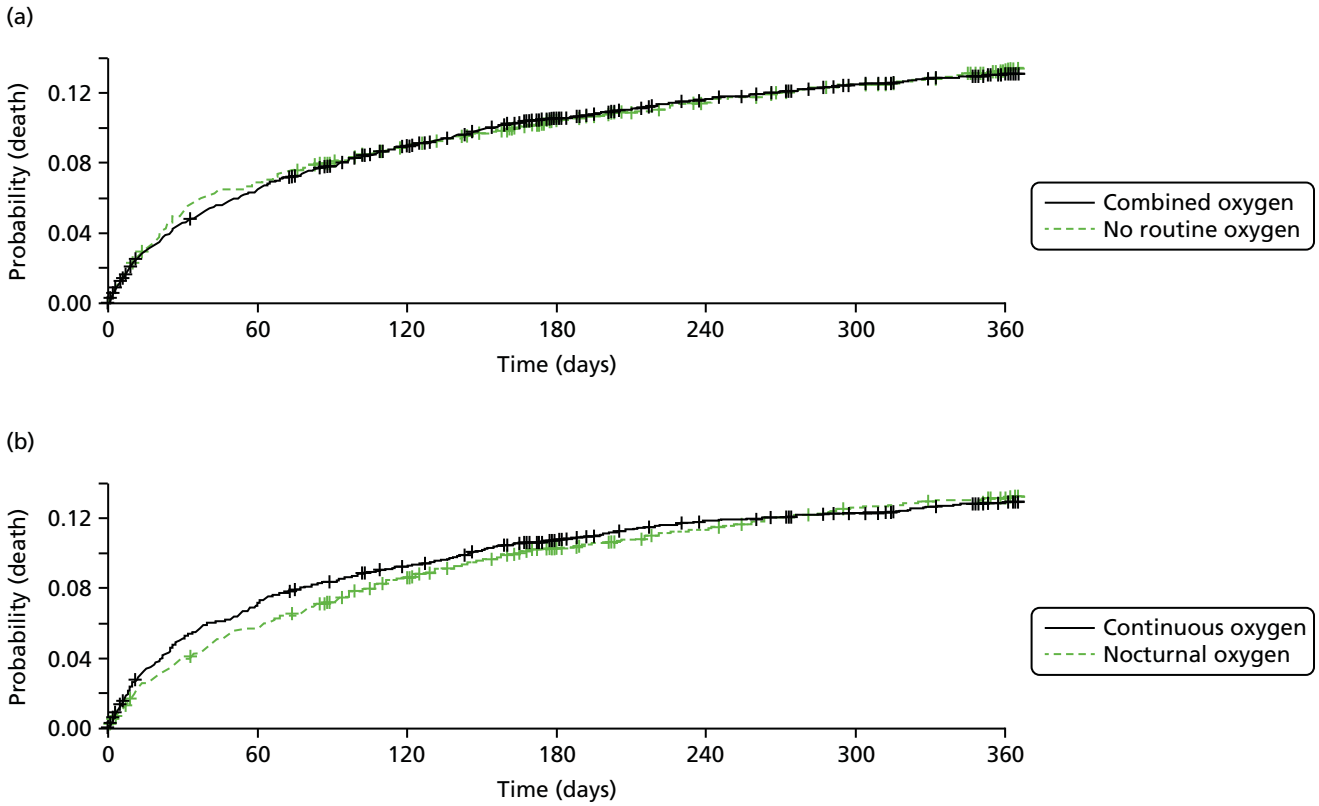

FIGURE 7 Kaplan–Meier survival graph comparing (a) oxygen (combined) with control (no ROS) at 365 days; and (b) continuous compared with nocturnal oxygen.

Functional outcomes

Figure 8 shows the mean mRS score at 3, 6 and 12 months. There was no change in the level of disability over the 3-, 6- and 12-month follow-up assessment points in any of the three groups. The proportion of patients in each mRS score category is shown in *Figure 9* for the combined oxygen group compared with the control group and in *Figure 10* for the continuous oxygen group compared with the nocturnal oxygen group. Oxygen has no effect on the level of disability at any time point, whether given continuously or at night only.

The number of patients who are alive and independent was similar in all three treatment groups and did not change with time (52%, 53% and 53%, respectively, at each of the three time points). Performance of activities of daily living (BI), ability to conduct extended activities of daily living (NEADL), and quality of life (EQ-5D-3L) were no different between the combined oxygen groups or between continuous and nocturnal oxygen at 90, 180 and at 365 days and were similar at each of the three time points (*Table 13*).

Outcomes considered important by stroke survivors

Outcomes considered important by stroke survivors during the pre-study focus group meetings (sleep, speech and memory) are shown in *Table 13*. There was also no difference in these outcomes between the continuous oxygen, nocturnal oxygen and control groups. At 90 days, 87% had no significant speech problems and 65% considered their sleep as good as before the stroke, but only 44% reported their memory as being as good as before the stroke. The data were similar at 180 and 365 days.

Length of hospital stay and readmissions

Data on length of stay were available for 2435 (91%), 2401 (90%) and 2446 (92%) of participants in the continuous oxygen, nocturnal oxygen and control groups. The mean (SD) length of stay in hospital was 18.6 days (50.9 days), 18.6 days (52.0 days) and 18.0 days (56.4 days), respectively (*Table 14*). The rate of readmissions (*Table 15*) increased with time, but was similar for all three treatment groups (14%, 17% and 20% at 3, 6 and 12 months, respectively).

Place of abode

Details of place of abode throughout the follow-up period are shown in *Table 15*. The proportion of patients living in their own homes, with relatives, in residential nursing, or continuing care homes was similar in all three groups. The proportion of participants living in their own homes or with family members was 76%, 74% and 68% at 3, 6 and 12 months. Only a few patients were residing in institutions (care home, nursing home or continuing NHS care) at each of the three time points (7%, 7% and 6%, respectively).

Blinding

Details of who completed the follow-up questionnaires, and whether or not the person completing the questionnaire remembers the treatment the participant was allocated to, are presented in *Table 16*. The proportion of participants who completed the follow-up questionnaires personally and unaided by another person was 33%, 29% and 28% at 3, 6 and 12 months. The proportions were similar for all three groups. As participants were not blinded to the intervention, we included a question at follow-up to assess whether or not they remembered which treatment group they were in. At 3 months, 49%, 35% and 45% in the continuous oxygen group, the nocturnal oxygen group and the control group, respectively, remembered their allocation correctly. At 6 months, 46%, 32% and 41%, respectively, remembered allocation correctly, and at 12 months correct memory of allocation was still recorded in 41%, 28% and 35% of participants.

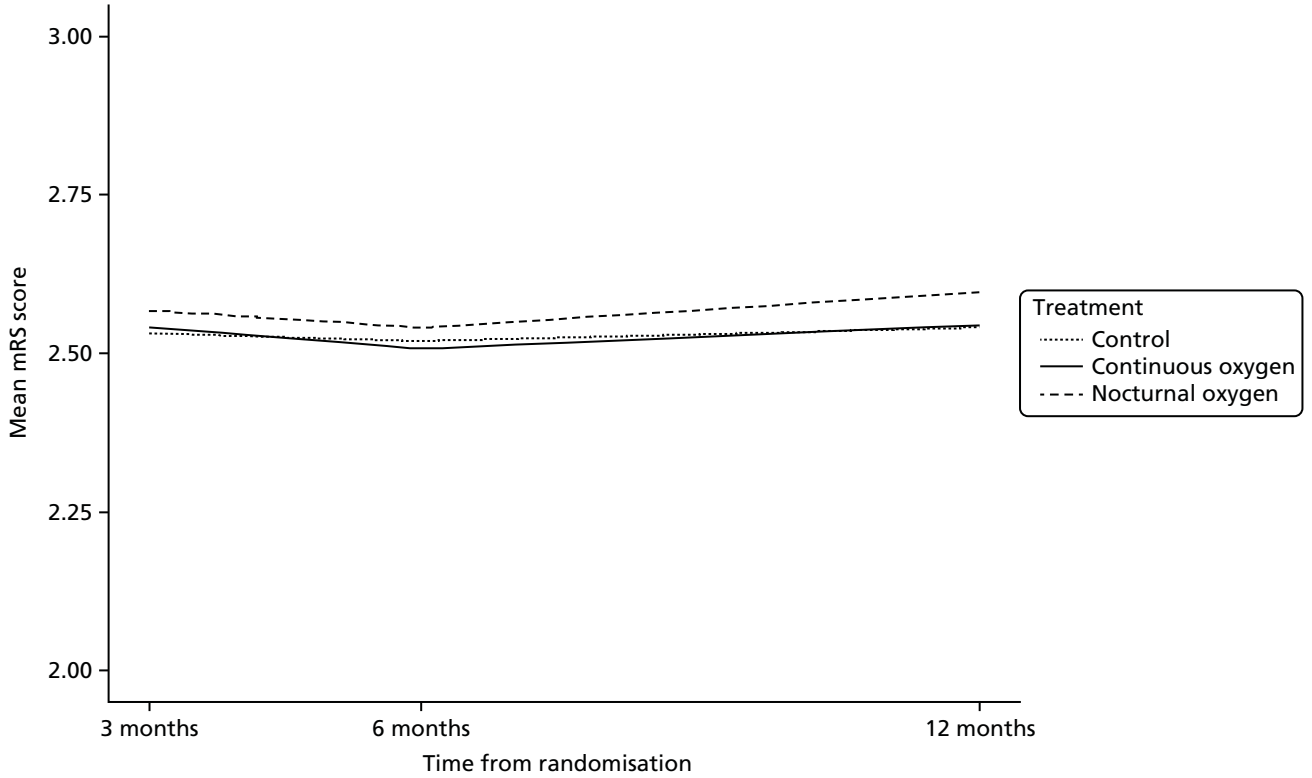

FIGURE 8 Modified Rankin Scale score at 3, 6 and 12 months.

(a)

	mRs	0	1	2	3	4	5	6
Control	*n*	336	671	330	415	395	156	246
	Percentage	13	26	13	16	16	6	10
	mRs	0	1	2	3	4	5	6
Combined oxygen	*n*	605	1399	637	883	795	316	493
	Percentage	12	27	12	17	16	6	10

(b)

	mRs	0	1	2	3	4	5	6
Control	*n*	350	613	342	404	362	125	272
	Percentage	14	25	14	16	15	5	11
	mRs	0	1	2	3	4	5	6
Combined oxygen	*n*	670	1287	661	818	727	239	549
	Percentage	14	26	13	16	15	5	11

(c)

	mRs	0	1	2	3	4	5	6
Control	*n*	344	563	308	333	340	101	279
	Percentage	15	25	14	15	15	4	12
	mRs	0	1	2	3	4	5	6
Combined oxygen	*n*	620	1225	549	729	700	212	554
	Percentage	13	27	12	16	15	5	12

FIGURE 9 Functional outcome of the combined (continuous and nocturnal) oxygen group compared with the control group at (a) 3; (b) 6; and (c) 12 months post randomisation.

(a)

Continuous oxygen	mRs	0	1	2	3	4	5	6
	n	313	690	322	461	376	148	257
	Percentage	12	27	12	18	15	6	10
Nocturnal oxygen	mRs	0	1	2	3	4	5	6
	n	292	709	315	422	419	168	236
	Percentage	11	28	12	17	16	7	9

(b)

Continuous oxygen	mRs	0	1	2	3	4	5	6
	n	355	620	338	416	352	114	280
	Percentage	14	25	14	17	14	5	11
Nocturnal oxygen	mRs	0	1	2	3	4	5	6
	n	315	667	323	402	375	125	269
	Percentage	13	27	13	16	15	5	11

(c)

Continuous oxygen	mRs	0	1	2	3	4	5	6
	n	317	617	282	356	342	101	285
	Percentage	14	27	12	15	16	4	12
Nocturnal oxygen	mRs	0	1	2	3	4	5	6
	n	303	608	267	373	358	111	269
	Percentage	13	26	12	16	16	5	12

FIGURE 10 Functional outcome of the continuous oxygen group compared with the nocturnal only oxygen group at (a) 3; (b) 6; and (c) 12 months post randomisation.

TABLE 13 Secondary outcomes at 3, 6 and 12 months

Variable	Time point								
	3 months			6 months			12 months		
	Continuous oxygen ($n = 2668$)	Nocturnal oxygen ($n = 2667$)	Control ($n = 2668$)	Continuous oxygen ($n = 2668$)	Nocturnal oxygen ($n = 2667$)	Control ($n = 2668$)	Continuous oxygen ($n = 2668$)	Nocturnal oxygen ($n = 2667$)	Control ($n = 2668$)
Death by follow-up time point[a]	257 (10.0%), $n = 2567$	236 (9.2%), $n = 2561$	246 (9.7%), $n = 2549$	280 (11.3%), $n = 2475$	269 (10.9%), $n = 2476$	272 (11.0%), $n = 2468$	285 (12.4%), $n = 2300$	269 (11.8%), $n = 2289$	279 (12.3%), $n = 2268$
Death by 90 days[a] (date)	222 (8.7%), $n = 2566$	194 (7.6%), $n = 2565$	214 (8.4%), $n = 2550$	–	–	–	–	–	–
Alive and independent[a]	1325 (51.6%), $n = 2567$	1316 (51.4%), $n = 2561$	1337 (52.5%), $n = 2549$	1313 (53.1%), $n = 2475$	1305 (52.7%), $n = 2476$	1305 (52.9%), $n = 2468$	1216 (52.9%), $n = 2300$	1178 (51.5%), $n = 2289$	1215 (53.6%), $n = 2268$
Living at home[a]	1961 (85.8%), $n = 2285$	1947 (84.8%), $n = 2295$	1947 (85.4%), $n = 2279$	1910 (87.6%), $n = 2181$	1932 (88.0%), $n = 2196$	1888 (86.4%), $n = 2184$	1774 (88.4%), $n = 2006$	1766 (88.0%), $n = 2007$	1728 (87.1%), $n = 1983$
Barthel ADL index [0 (worst) to 100 (best)][b]	70.2 (68.7 to 71.8), $n = 2169$	71.1 (69.6 to 72.6), $n = 2194$	70.9 (69.3 to 72.4), $n = 2186$	71.4 (69.9 to 72.9), $n = 2175$	70.9 (69.4 to 72.5), $n = 2158$	71.1 (69.6 to 72.7), $n = 2158$	70.3 (68.6 to 72.0), $n = 1945$	70.1 (68.5 to 71.7), $n = 1963$	70.7 (69.0 to 72.3), $n = 1954$
Nottingham Extended ADL [0 (worst) to 21 (best)][b]	9.66 (9.38 to 9.93), $n = 2520$	9.54 (9.26 to 9.81), $n = 2501$	9.77 (9.49 to 10.05), $n = 2507$	9.85 (9.57 to 10.14), $n = 2442$	9.74 (9.45 to 10.02), $n = 2442$	10.01 (9.72 to 10.30), $n = 2426$	10.09 (9.79 to 10.39), $n = 2254$	9.80 (9.50 to 10.10), $n = 2239$	10.15 (9.84 to 10.45), $n = 2218$
Quality of Life (EQ-5D-3L) [–0.59 (worst) to 1 (best)][b]	0.44 (0.42 to 0.46), $n = 2413$	0.44 (0.42 to 0.46), $n = 2428$	0.43 (0.41 to 0.45), $n = 2407$	0.42 (0.40 to 0.44), $n = 2338$	0.43 (0.41 to 0.45), $n = 2353$	0.43 (0.40 to 0.45), $n = 2328$	0.41 (0.39 to 0.43), $n = 2103$	0.42 (0.40 to 0.45), $n = 2110$	0.41 (0.39 to 0.44), $n = 2081$
Quality of life (EQ-VAS) [0 (worst) to 100 (best)][b]	55.4 (54.2 to 56.7), $n = 2251$	55.7 (54.4 to 56.9), $n = 2216$	55.5 (54.2 to 56.7), $n = 2208$	56.9 (55.6 to 58.2), $n = 2164$	57.1 (55.8 to 58.4), $n = 2148$	56.9 (55.6 to 58.2), $n = 2133$	56.1 (54.7 to 57.6), $n = 1900$	57.0 (55.6 to 58.4), $n = 1903$	56.7 (55.3 to 58.1), $n = 1872$
Sleep as good as before the stroke[a]	1407 (64%), $n = 2194$	1436 (65%), $n = 2208$	1419 (65%), $n = 2182$	1339 (64%), $n = 2103$	1368 (65%), $n = 2114$	1363 (65%), $n = 2100$	1249 (66%), $n = 1888$	1243 (64%), $n = 1930$	1196 (63%), $n = 1889$
No significant speech problems[a]	1957 (88%), $n = 2229$	1957 (87%), $n = 2246$	1939 (87%), $n = 2241$	1923 (89%), $n = 2152$	1921 (89%), $n = 2163$	1900 (89%), $n = 2140$	1739 (90%), $n = 1940$	1749 (90%), $n = 1954$	1750 (91%), $n = 1925$
Memory as good as before the stroke[a]	981 (44%), $n = 2222$	1000 (45%), $n = 2224$	971 (44%), $n = 2220$	888 (42%), $n = 2127$	914 (43%), $n = 2132$	888 (42%), $n = 2110$	800 (42%), $n = 1920$	782 (41%), $n = 1930$	762 (40%), $n = 1893$

ADL, Activities of daily living; EQ-5D-3L, European Quality of Life-5 Dimensions, three levels; VAS, visual analogue scale.
a Data are given as numbers and percentages.
b Data are given as means and 99% CIs.
Alive and independent is a mRS score of two or fewer.

TABLE 14 Length of hospital stay

Length of stay in hospital	Trial arm		
	Continuous oxygen ($N = 2668$)	Nocturnal oxygen ($N = 2667$)	Control ($N = 2668$)
Randomisation to final discharge, mean (SD)	18.6 days (50.9 days)	18.6 days (52.0 days)	18.0 days (56.4 days)
No data, *n* (%)	233 (9%)	266 (10%)	222 (8%)

Co-enrolment in other research studies

Participants in SO_2S were permitted to co-enrol in other studies, if they wished, and if other studies were available. Participants were asked if they were enrolled in other studies at each of the three follow-up points. The results are shown in *Table 16*. The proportion of participants who reported enrolment in other studies was low, with no differences between treatment groups, and did not change over time (3%, 4% and 3% at 3, 6 and 12 months, respectively).

Safety outcomes

The number of patients who experienced at least one serious adverse event at 90, 180 and 365 days is shown in *Table 17*. Details of serious adverse events within the first 90 days are given in *Table 18*.

Health economics analysis results

A total of 7898 trial participants (no ROS, $n = 2629$; continuous ROS, $n = 2636$; and nocturnal ROS, $n = 2633$) formed the data set for the analysis. All base-case analyses were conducted on the imputed data set. The analyses for the comparison of ROS with no ROS are presented first, followed by all analyses for the comparison of continuous ROS and nocturnal ROS with no ROS and, finally, the deterministic sensitivity analyses for ROS compared with no ROS.

Base-case analysis

Comparison of routine oxygen supplementation with no routine oxygen supplementation

Table 19 presents the mean outcomes per patient in terms of hospital stay, home time, EQ-5D-3L scores and QALYs. Both mean hospital stay and home time were marginally higher in the ROS group, but by less than half a day. There were no differences in mean EQ-5D-3L scores at 3, 6 and 12 months and the difference in QALYs was very small, at 0.0004 QALYs, and not significant. *Table 20* presents disaggregated mean (SD) health-care costs per patient for trial oxygen and additional oxygen, acute stay costs, readmissions and long-term care, as well as total health-care costs. As expected, oxygen treatment costs were higher in the ROS arm, with all other costs slightly higher for ROS, and £206 (95% CI –£283 to £695) higher overall, compared with no ROS.

The cost-effectiveness analysis presented in *Table 21* shows that it costs an additional £71 to gain a day of home time. The CUA gave an ICER of £463,338 per QALY gained (*Table 22*). The cost-effectiveness plane in *Figure 11* demonstrates the uncertainty around both costs and QALY differences, with points in all four quadrants. The corresponding CEAC in *Figure 12* shows a 27% probability of ROS being cost-effective compared with no ROS if society was willing to pay up to £20,000 per additional QALY, also suggesting ROS is not cost-effective.

TABLE 15 Details of current abode and readmission data for each of the 3-, 6- and 12-month follow-ups

Variable	Time point								
	3 months			6 months			12 months		
	Continuous oxygen (*N* = 2668)	Nocturnal oxygen (*N* = 2667)	Control (*N* = 2668)	Continuous oxygen (*N* = 2668)	Nocturnal oxygen (*N* = 2667)	Control (*N* = 2668)	Continuous oxygen (*N* = 2668)	Nocturnal oxygen (*N* = 2667)	Control (*N* = 2668)
Where do you live now?									
In own home, *n* (%)	1961 (73.5%)	1948 (73.0%)	1947 (73.0%)	1911 (71.7%)	1932 (72.4%)	1888 (70.8%)	1774 (66.5%)	1766 (66.2%)	1728 (64.8%)
In the home of a relative, *n* (%)	86 (3.2%)	79 (3.0%)	62 (2.3%)	78 (2.9%)	69 (2.6%)	61 (2.3%)	67 (2.5%)	54 (2.0%)	56 (2.1%)
In a residential home, *n* (%)	62 (2.3%)	63 (2.4%)	73 (2.7%)	57 (2.1%)	57 (2.1%)	75 (2.8%)	54 (2.0%)	53 (2.0%)	72 (2.7%)
In a nursing home, *n* (%)	70 (2.6%)	114 (4.0%)	111 (4.2%)	97 (3.6%)	114 (4.3%)	120 (4.5%)	92 (3.45%)	118 (4.4%)	109 (4.09%)
In a continuing care home, *n* (%)	37 (1.4%)	34 (1.3%)	25 (0.9%)	15 (0.6%)	8 (0.3%)	9 (0.3%)	6 (0.2%)	1 (0.04%)	5 (0.19%)
Not left hospital yet since stroke, *n* (%)	60 (2.3%)	50 (2.0%)	43 (1.6%)	7 (0.3%)	4 (0.1%)	12 (0.5%)	1 (0.04%)	2 (0.07%)	1 (0.04%)
Other, *n* (%)	9 (0.3%)	9 (0.3%)	18 (0.7%)	17 (0.6%)	12 (0.5%)	19 (0.7%)	12 (0.5%)	13 (0.49%)	12 (0.4%)
Withdrawn or no data, *n* (%)	383 (14.4%)	370 (14.0%)	389 (14.6%)	486 (18.2%)	471 (17.7%)	484 (18.1%)	662 (24.81%)	660 (24.8%)	685 (25.68%)
Have you been admitted to hospital again for any reason after you were discharged?									
Yes, *n* (%)	379 (14%)	356 (13%)	380 (14%)	456 (17%)	457 (17%)	434 (16%)	540 (20%)	550 (21%)	546 (21%)
No, *n* (%)	1831 (69%)	1883 (71%)	1850 (69%)	1717 (64%)	1732 (65%)	1743 (65%)	1456 (55%)	1449 (54%)	1423 (53%)
No data, *n* (%)	458 (17%)	428 (16%)	438 (17%)	495 (19%)	478 (18%)	491 (19%)	672 (25%)	668 (25%)	699 (26%)
If yes, how many times?									
Once, *n* (%)	285 (11%)	272 (10%)	296 (11%)	305 (11%)	322 (12%)	295 (11%)	341 (13%)	358 (13%)	363 (14%)
More than once, *n* (%)	91 (3%)	80 (3%)	83 (3%)	145 (5%)	131 (5%)	134 (5%)	195 (7%)	186 (7%)	181 (7%)
No data, *n* (%)	3 (0.1%)	4 (0.1%)	1 (< 0.1%)	6 (0.2%)	4 (0.1%)	5 (0.2%)	4 (0.1%)	6 (0.2%)	2 (0.1%)

TABLE 16 Patient recollection of trial intervention, participation in other trials and details of who completed the follow-up questionnaires for each follow-up time point

Variable	Time points								
	3 months			6 months			12 months		
	Continuous oxygen (*N* = 2668)	Nocturnal oxygen (*N* = 2667)	Control (*N* = 2668)	Continuous oxygen (*N* = 2668)	Nocturnal oxygen (*N* = 2667)	Control (*N* = 2668)	Continuous oxygen (*N* = 2668)	Nocturnal oxygen (*N* = 2667)	Control (*N* = 2668)
Can you remember which of the treatments you were given as part of the trial?									
Yes (correct), *n* (%)	1314 (49%)	942 (35%)	1194 (45%)	1228 (46%)	849 (32%)	1082 (41%)	1084 (41%)	749 (28%)	940 (35%)
Yes (incorrect), *n* (%)	222 (8%)	530 (20%)	105 (4%)	223 (8%)	588 (22%)	120 (4%)	185 (7%)	515 (19%)	117 (5%)
I do not know, *n* (%)	545 (21%)	621 (23%)	749 (28%)	537 (20%)	577 (22%)	747 (28%)	515 (19%)	567 (21%)	699 (26%)
No data, *n* (%)	587 (22%)	574 (22%)	620 (23%)	680 (26%)	653 (24%)	719 (27%)	884 (33%)	836 (32%)	912 (34%)
Have you taken part in any other research trials since the start of this study?									
Yes, *n* (%)	78 (3%)	85 (3%)	87 (3%)	95 (4%)	78 (3%)	116 (4%)	75 (3%)	87 (3%)	98 (4%)
No, *n* (%)	1870 (70%)	1856 (70%)	1838 (69%)	1815 (68%)	1870 (70%)	1775 (67%)	1711 (64%)	1704 (64%)	1673 (63%)
No data, *n* (%)	720 (27%)	726 (27%)	743 (28%)	758 (28%)	719 (27%)	777 (29%)	882 (33%)	876 (33%)	897 (33%)
Who completed the questionnaire?									
Patient, *n* (%)	888 (33.3%)	840 (31.5%)	873 (32.7%)	810 (30.4%)	763 (28.6%)	783 (29.3%)	742 (27.8%)	760 (28.5%)	767 (28.8%)
Patient with some help, *n* (%)	266 (10.0%)	238 (8.9%)	233 (8.7%)	192 (7.2%)	187 (7.0%)	166 (6.2%)	187 (7.0%)	176 (6.6%)	164 (6.1%)
A relative, friend or carer, *n* (%)	405 (15.2%)	442 (16.6%)	393 (14.7%)	312 (11.7%)	328 (12.3%)	325 (12.2%)	298 (11.2%)	303 (11.4%)	296 (11.1%)
Researcher over the telephone, *n* (%)	657 (24.6%)	692 (26.0%)	720 (27%)	824 (30.9%)	872 (32.7%)	845 (31.7%)	709 (26.6%)	715 (26.8%)	701 (26.3%)
Researcher in hospital clinic, *n* (%)	18 (0.7%)	22 (0.8%)	13 (0.5%)	10 (0.4%)	7 (0.3%)	18 (0.7%)	8 (0.3%)	4 (0.1%)	10 (0.4%)
Other, *n* (%)	15 (0.5%)	17 (0.6%)	16 (0.6%)	12 (0.4%)	12 (0.4%)	13 (0.5%)	12 (0.4%)	18 (0.7%)	6 (0.2%)
No data, *n* (%)	419 (15.7%)	416 (15.6%)	420 (15.8%)	508 (19.0%)	498 (18.7%)	518 (19.4%)	712 (26.7%)	691 (25.9%)	724 (27.1%)

TABLE 17 The number (proportion) of patients who experienced at least one serious adverse event

Variable	*n* (*N* = 8003)	Trial arm			Combined oxygen vs. control, OR (99% CI)	Combined oxygen vs. control, *p*-value	Continuous vs. nocturnal, OR (95% CI)	Continuous vs. nocturnal, *p*-value
		Continuous oxygen (*N* = 2668), *n* (%)	Nocturnal oxygen (*N* = 2667), *n* (%)	Control (*N* = 2668), *n* (%)				
Number of patients with at least one SAE by 90 days	964	348 (13%), *n* = 2668	294 (11%), *n* = 2667	322 (12%), *n* = 2668	1.00 (0.83 to 1.20)	1.0	1.21 (0.97 to 1.51)	0.02
Number of patients with at least one SAE by 180 days	1385	485 (18%), *n* = 2668	442 (17%), *n* = 2667	458 (17%), *n* = 2668	1.02 (0.86 to 1.19)	0.8	1.12 (0.93 to 1.35)	0.1
Number of patients with at least one SAE by 365 days	2034	708 (27%), *n* = 2668	675 (25%), *n* = 2667	651 (24%), *n* = 2668	1.08 (0.94 to 1.25)	0.1	1.07 (0.91 to 1.25)	0.3

SAE, serious adverse event.

TABLE 18 Serious adverse events by event categories

Variable	Trial arm			Total (*N* = 8003)
	Continuous oxygen (*N* = 2668), *n*	Nocturnal oxygen (*N* = 2667), *n*	Control (*N* = 2668), *n*	
Cardiovascular	54	48	37	139
DVT	4	3	3	10
PE	18	6	9	33
Central nervous system	177	141	178	496
Agitation	3	0	0	3
Anxiety	1	1	2	4
Central nervous system other	3	5	2	10
Cerebral oedema	10	2	6	18
Complication of initial stroke	36	26	23	85
Confusion	2	3	0	5
Dementia	0	0	2	2
Extension of initial stroke	34	32	45	111
Functional symptoms	0	2	0	2
Haemorrhagic transformation	8	8	16	32
Headache	1	3	2	6
Intracerebral bleed	12	8	4	24
Intracranial/extracerebral bleed	1	1	4	6
Recurrent stroke	41	36	42	119
Seizure	10	7	18	35
TIA	13	7	10	30
Vertigo	1	0	0	1
Vomiting	1	0	2	3
Cutaneous	1	0	0	1
Gastrointestinal	15	9	13	37
Genitourinary	11	10	21	42
Haematological	0	1	0	1
Immunological	0	0	0	0
Miscellaneous	40	33	37	110
Respiratory	76	84	97	257
Chest infection	2	4	3	9
Hypoxia	3	1	6	10
Pneumonia	69	78	87	234
Respiratory other	2	1	1	4
Oxygen-related	0	0	0	0
Drying of mucous membranes	0	0	0	0
Respiratory depression	0	0	0	0
Other	30	23	23	76
Total	426	358	418	1202

DVT, deep vein thrombosis; PE, pulmonary embolism.
This table gives the number and categories of serious adverse events reported up to 90 days after randomisation.

TABLE 19 Mean outcomes per patient by treatment group over 12 months

Variable	Intervention	
	No ROS (*N* = 2629)	ROS (*N* = 5269)
Mean hospital stay (days) (95% CI)	18.4 (17.7 to 19)	18.7 (17.9 to 19.5)
Mean home time (days) (95% CI)	313.0 (310.4 to 315.7)	313.4 (310.2 to 136.5)
EQ-5D-3L scores [mean (SD)]		
Baseline	0	0
3 months	0.48 (0.38)	0.48 (0.37)
6 months	0.48 (0.37)	0.48 (0.37)
12 months	0.46 (0.37)	0.46 (0.37)
Total QALYs over 12 months	0.4133 (0.31)	0.4137 (0.30)
Difference in QALYs (95% CI)	0.0004 (–0.0139 to 0.0148)	

TABLE 20 Mean (95% CI) costs (£) per patient by treatment group over 12 months

Cost category	Intervention	
	No ROS (*N* = 2629)	ROS (*N* = 5629)
Trial prescribed oxygen	0.65 (0.42 to 0.94)	72.89 (72.62 to 73.15)
Additional oxygen	5.52 (4.76 to 6.37)	9.40 (8.44 to 10.32)
Total oxygen treatment	6.18 (5.40 to 7.05)	82.29 (81.30 to 83.38)
Acute care costs	5130 (4856 to 5406)	5196 (5008 to 5418)
Readmission	978 (929 to 1032)	986 (951 to 1022)
Stroke care after discharge	6587 (6310 to 6865)	6643 (6447 to 6835)
Total cost	12,702 (12,309 to 13,115)	12,908 (12,619 to 13,183)
Mean difference (95% CI)	206 (–283 to 695)	

TABLE 21 Cost-effectiveness analysis

Intervention	Mean costs (£)	Cost difference (£)	Mean days of home time	Outcome difference (days)	ICER (£/day of home time gained)
No ROS	6.2	–	312.28	–	–
ROS	82.3	76.1	313.36	1.08	70.74

TABLE 22 Cost–utility analysis

Intervention	Mean costs (£)	Cost difference (£)	Mean QALYs	QALY difference	ICER (£/QALY gained)
No ROS	12,702	–	0.4133	–	–
ROS	12,908	206	0.4137	0.0004	463,338

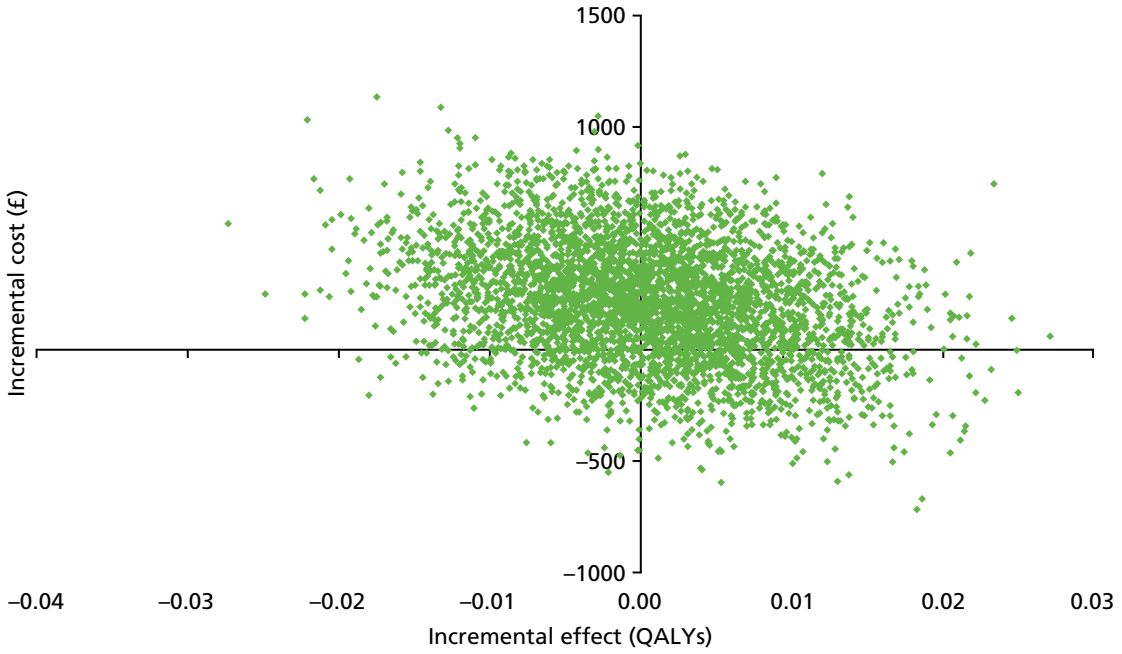

FIGURE 11 Cost-effectiveness plane for ROS compared with no ROS.

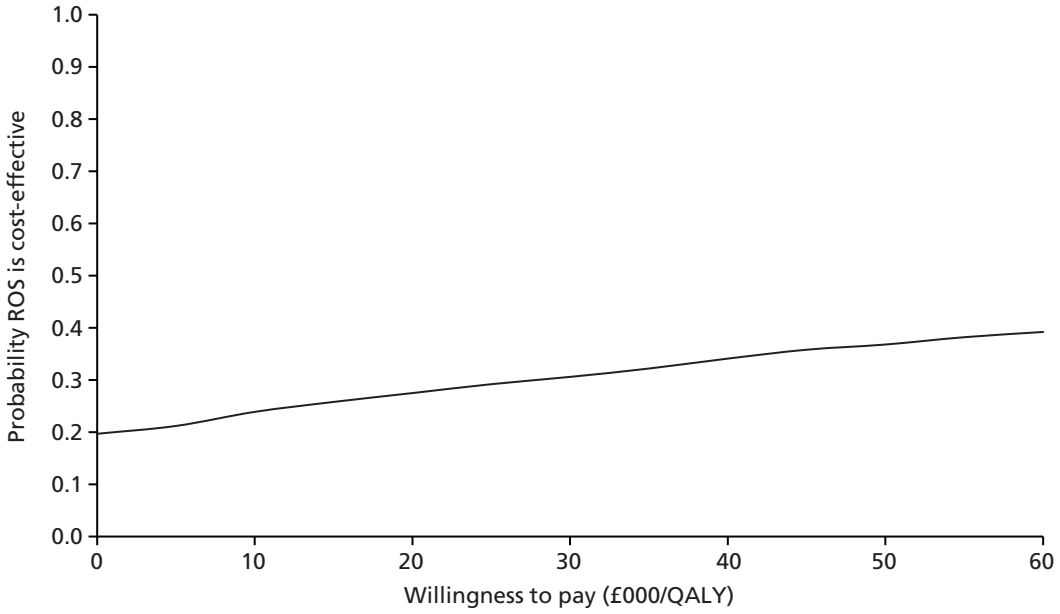

FIGURE 12 Cost-effectiveness acceptability curve for ROS compared with no ROS.

Comparison of continuous routine oxygen supplementation and nocturnal routine oxygen supplementation with no routine oxygen supplementation

Table 23 presents the mean outcomes per patient in terms of hospital stay, home time, EQ-5D-3L scores and QALYs for all three trial arms. Mean hospital stay was the greatest in the nocturnal ROS group. Home time was lowest in the nocturnal ROS group and highest for continuous ROS, by almost 3 days compared with no ROS. There was almost no difference in mean EQ-5D-3L scores at 3, 6 and 12 months. Overall QALYs for nocturnal ROS were slightly lower (mean difference –0.0023 QALYs) than for no ROS, and slightly higher than for continuous ROS (mean difference 0.0032 QALYs), but in both cases differences were very small and non-significant. *Table 24* shows the disaggregated mean (SD) health-care costs per patient for both trial and additional oxygen, acute stay costs, readmissions and long-term care, as well as

TABLE 23 Mean outcomes per patient by treatment group over 12 months

Variable	Intervention		
	No ROS (*N* = 2629)	Nocturnal ROS (*N* = 2633)	Continuous ROS (*N* = 2636)
Mean hospital stay (days) (95% CI)	18.4 (17.7 to 19.0)	19.0 (17.9 to 20.1)	18.5 (17.4 to 19.6)
Mean home time (days) (95% CI)	313.0 (310.4 to 315.7)	310.9 (306.6 to 315.6)	315.9 (311.4 to 320.2)
EQ-5D-3L scores, mean (SD)			
Baseline	0	0	0
3 months	0.48 (0.38)	0.48 (0.37)	0.48 (0.37)
6 months	0.48 (0.37)	0.47 (0.37)	0.48 (0.36)
12 months	0.46 (0.37)	0.46 (0.37)	0.46 (0.36)
Mean (SD) total QALYs over 12 months	0.4133 (0.31)	0.4109 (0.31)	0.4164 (0.30)
Difference in QALYs (95% CI) (vs. no ROS)	–	–0.0023 (–0.018 to 0.014)]	0.0032 (–0.0132 to 0.0019)

TABLE 24 Mean (95% CI) costs (£) per participant by treatment group over 12 months

Cost category	Intervention		
	No ROS (*N* = 2629)	Nocturnal ROS (*N* = 2633)	Continuous ROS (*N* = 2636)
Trial prescribed oxygen	0.65 (0.42 to 0.94)	64.32 (64.12 to 64.50)	81.45 (81.21 to 81.67)
Additional oxygen	5.52 (4.76 to 6.37)	3.83 (3.27 to 4.46)	14.97 (13.32 to 16.73)
Total oxygen treatment	6.18 (5.40 to 7.05)	68.15 (67.50 to 68.79)	96.42 (94.61 to 98.26)
Acute care costs	5130 (4855 to 5404)	5125 (4862 to 5406)	5265 (4990 to 5583)
Readmission	978 (929 to 1032)	976 (924 to 1030)	997 (948 to 1052)
Stroke care after discharge	6587 (6310 to 5406)	6697 (6420 to 6984)	6588 (6305 to 6855)
Total cost	12,702 (12,309 to 13,115)	12,867 (12,471 to 13,286)	12,948 (12,523 to 13,347)
Mean difference (95% CI) (vs. no ROS)	–	165 (–393 to 725)	246 (–322 to 814)

total health-care costs. Oxygen treatment costs were highest in the continuous ROS arm, and there were small differences in other health-care costs between trial arms. Total health care costs were higher in both ROS arms and highest in the continuous ROS arm, £246 (95% CI –£322 to £814) higher overall compared with no ROS.

The cost-effectiveness analysis presented in *Table 25* shows that nocturnal ROS is dominated by no ROS. An intervention is dominated if it is more costly but less effective. Here, the outcomes for nocturnal ROS are worse, with fewer days of home time but at a higher cost than no ROS. Continuous ROS costs £25 per extra day of home time gained compared with no ROS. In the CUA, nocturnal ROS was again dominated because of lower QALYs and higher costs. Continuous ROS had an ICER of £76,997 per QALY gained, well above standard NICE willingness-to-pay thresholds of £20,000 to £30,000 per QALY (*Table 26*). The cost-effectiveness plane in *Figure 13* displays a high level of uncertainty in both cost and QALY differences, with points in all four quadrants, and the corresponding CEAC (*Figure 14*) shows a 31% probability of continuous ROS being cost-effective compared with no ROS at a £20,000 per additional QALY threshold, suggesting that it is not a cost-effective intervention.

TABLE 25 Cost-effectiveness analysis

Intervention	Mean costs (£)	Cost difference (£)	Mean days of home time	Outcome difference (days)	ICER (£/day of home time gained)
No ROS	6.2	–	312.28	–	–
Nocturnal ROS	68.2	62.0	310.87	–1.41	Dominated
Continuous ROS	96.4	90.2	315.87	3.59	25.13

TABLE 26 Cost–utility analysis

Intervention	Mean costs (£)	Cost difference (£)	Mean QALYs	QALY difference	ICER (£/QALY gained)
No ROS	12,702	–	0.4133	–	–
Nocturnal ROS	12,867	165	0.4109	–0.0023	Dominated
Continuous ROS	12,948	246	0.4164	0.0032	76,997

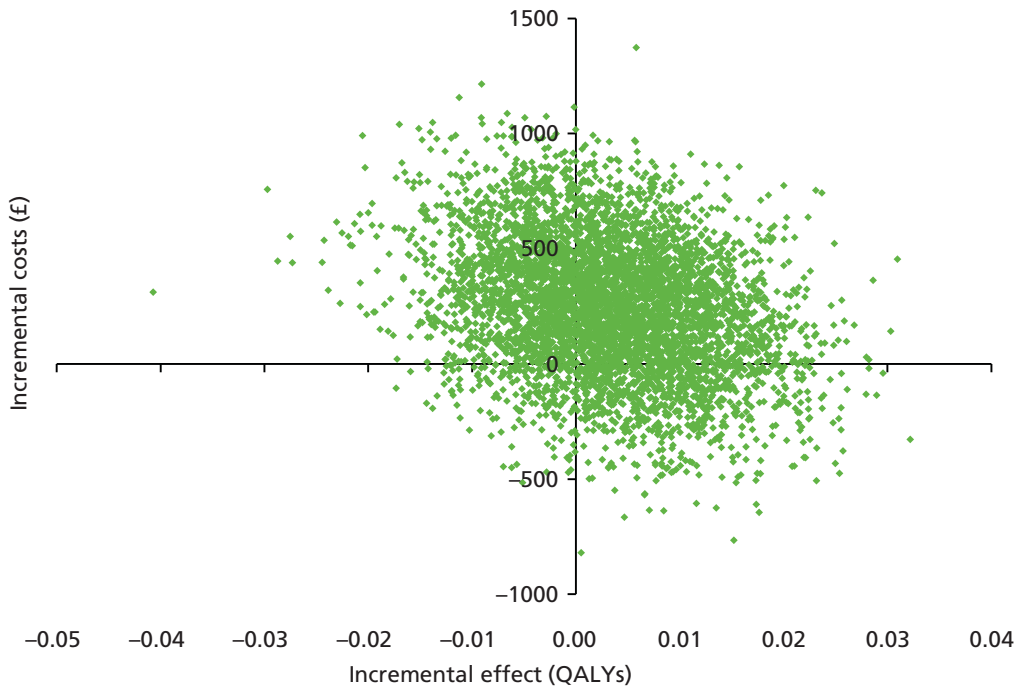

FIGURE 13 Cost-effectiveness plane for continuous ROS compared with no ROS.

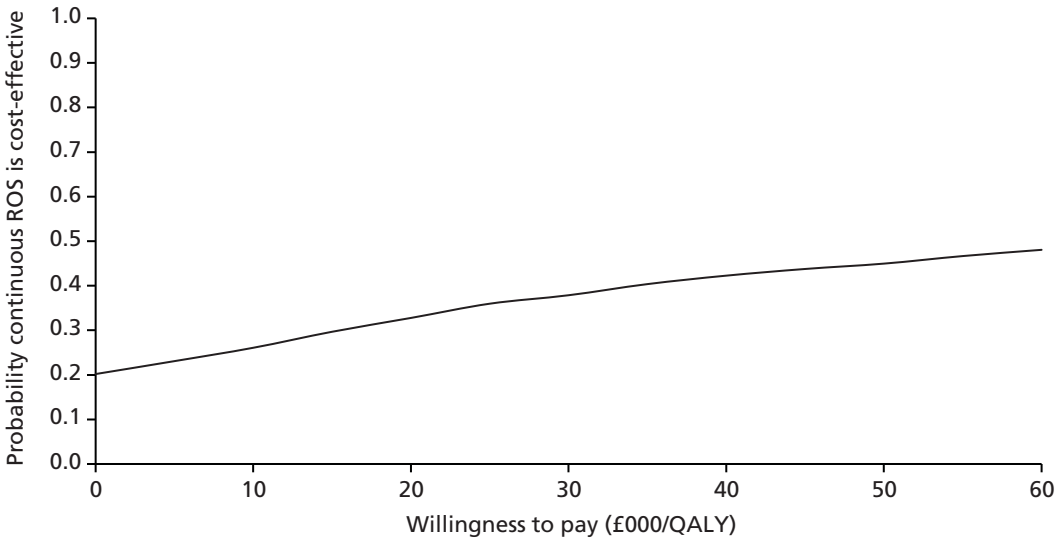

FIGURE 14 Cost-effectiveness acceptability curve for continuous ROS compared with no ROS.

Sensitivity analysis

Deterministic sensitivity analysis was undertaken for the CUA for ROS versus no ROS. This was to assess (1) the impact on results of changing the health care cost inputs and (2) an alternative approach to valuing baseline quality of life. Three main types of cost (oxygen, acute care, long-term care) were individually changed by increasing and then decreasing the base-case value by 20% (*Table 27*). The difference in costs between ROS and no ROS changed very little across the board and all ICERs were over £400,000 per QALY gained. The differences in ICERs do appear to be large; however, this is a result of the sensitivity of the ICER to small changes in cost, owing to the extremely small difference in QALYs.

A further analysis was undertaken to look at the impact of applying a different method for valuing the baseline quality of life of patients (*Table 28*). The base-case assumed an EQ-5D-3L score of zero and a linear increase in quality of life to 3 months. The alternative analysis used the EQ-5D-3L value at 3 months for the baseline value. This increased the total mean QALYs over 12 months for both ROS and no ROS and the difference in QALYs also increased to 0.0008, but this is still a very small difference. The ICER decreased to £257,500 per QALY gained, still considerably higher than the cost per QALY threshold of £20,000 to £30,000 per QALY.

TABLE 27 Sensitivity analysis for costs (£) for the comparison between ROS vs. no ROS

Cost/outcome	Acute care costs increased by 20%		Acute care costs decreased by 20%		Total oxygen treatment cost increased by 20%		Total oxygen treatment cost decreased by 20%		Stroke care after discharge increased by 20%		Stroke care after discharge decreased by 20%	
	No ROS	ROS	No ROS	ROS	No ROS	ROS	No ROS	ROS	No ROS	ROS	No ROS	ROS
Mean cost	13,727	13,946	11,675	11,868	12,702	12,923	12,700	12,891	14,018	14,236	11,384	11,578
Cost difference	–	219	–	193	–	221	–	191	–	218	–	194
Mean QALYs	0.4133	0.4137	0.4133	0.4137	0.4133	0.4137	0.4133	0.4137	0.4133	0.4137	0.4133	0.4137
QALY difference	–	0.0004	–	0.0004	–	0.0004	–	0.0004	–	0.0004	–	0.0004
Cost per QALY	–	493,185	–	433,603	–	497,638	–	429,150	–	488,394	–	438,417

TABLE 28 Sensitivity analysis applying an alternative assumption for baseline EQ-5D-3L score

Intervention	Mean costs (£)	Cost difference (£)	Mean QALYs	QALY difference	ICER (£/QALY gained)
No ROS	12,702	–	0.4729	–	–
ROS	12,908	206	0.4737	0.0008	257,500

Chapter 4 Discussion

The Stroke Oxygen Study is, with 8003 participants enrolled, the largest UK acute stroke trial. Over 50% of all stroke services in the UK contributed to the study, making participants representative of typical UK stroke patients. The results of SO_2S show that routine low-dose oxygen supplementation after acute stroke does not improve early neurological recovery or long-term functional outcome. The observed lack of effect was consistent across all time points (1 week and 3, 6 and 12 months), all outcomes and all subgroups. There was no difference in outcome between the group given oxygen continuously and the group that was given oxygen at night only.

In the following sections potential reasons for lack of effect, limitations of the study, health economic aspects, what SO_2S adds to existing evidence, what remains unknown, and implications for treatment and research will be discussed.

Potential reasons for the observed lack of effect

Mismatch of baseline clinical and demographic characteristics

The large sample size ($n = 8003$) makes mismatch of baseline clinical characteristics highly unlikely. Further safeguards against mismatch were built into the protocol. Randomisation by minimisation including key prognostic factors (age, sex, living alone, normal verbal component of the GCS, ability to lift both arms, the ability to walk, routine oxygen treatment during ambulance transfer and baseline oxygen saturation) ensured equal distribution of these factors across the three treatment groups. Effectiveness of minimisation was monitored continuously during the course of the study via online minimisation reports. The results in *Table 6* confirm that there were no differences in demographics and baseline clinical characteristics between the three groups. The negative results of this study cannot be explained by a mismatch in baseline clinical characteristics.

The patients recruited to the study were not representative of acute stroke patients

To ensure that patients in SO_2S were representative of acute stroke patients, inclusion criteria both for participating centres and for patient enrolment were wide. This is the largest and highest recruiting acute stroke study in the UK. In total 136 centres, including both acute and hyperacute stroke units, participated in the study. This means that over 50% of stroke services in the UK enrolled patients into SO_2S. Stroke patients enrolled into clinical studies tend to have less severe neurological deficits than the overall stroke population unless the inclusion criteria specify that only severe patients can be included. Key reasons for this are both ethical constraints (it would not be ethical to include moribund patients who have nothing to gain from the trial intervention) and problems with obtaining informed consent in a patient group who have suffered a brain injury and are therefore often unable to make a fully informed decision. In spite of these unavoidable constraints, stroke severity in SO_2S was representative of the stroke population in the UK. Participants in SO_2S had a median NIHSS score of 5. While this seems low, it reflects patients admitted to acute stroke units. Data from 23,199 patients in the UK Sentinel Stroke National Audit Programme show a median NIHSS score of 4 for stroke patients in the UK.[82] The median NIHSS score of 127,950 patients with acute ischaemic stroke in the US Get with the Guidelines Register was 5,[83] as in SO_2S. A median NIHSS score of 5 was also recorded at baseline in a recently published Dutch study of antibiotic prophylaxis after stroke,[84] which had similarly wide inclusion criteria to those of SO_2S. This is a study of routine prophylactic oxygen supplementation in acute stroke. Patients with clinically significant hypoxia (e.g. oxygen saturations below 90%) who thus had indications for oxygen supplementation were not included. Our results therefore do not apply to clearly hypoxic patients. However, 717 of the participants had mild hypoxia (oxygen saturation below 95%) at the time of enrolment. The lack of benefit was the same in this subgroup as in patients who had normal or high-normal oxygen saturations at enrolment. While this study was not powered to examine this question, the results do not support the hypothesis that

patients with lower baseline oxygen saturations are more likely to benefit from oxygen treatment. While we have not conducted formal screening logs for this study, discussions with participating centres about barriers to recruitment identified the requirement to recruit within 24 hours of hospital admission and the need for informed consent as the main barriers to enrolment, while clinical indications for oxygen treatment were rarely a problem. Apart from the protocol-driven exclusion of hypoxic patients, the participants in this study were as representative of the general stroke patient population as it is possible to achieve in a clinical study.

The amount of oxygen given may have been insufficient

The dose of oxygen given in SO_2S was based on the results of a dose-ranging study and aimed to keep oxygen saturation within the normal range, avoiding both hyperoxia and hypoxia. The dose of oxygen given might have been too low. Studies of short-duration high-flow oxygen do not support this possibility but were too small to identify benefit or exclude harm.[30,85] The largest ($n = 85$) study of short-burst high-flow oxygen was terminated early because of excess mortality in the actively treated group,[86] but it cannot be excluded that this difference was a result of baseline imbalance in the study groups rather than a true effect of oxygen. All three studies tested oxygen for 12 hours or less. It remains unknown whether or not higher-flow oxygen given during the whole hyperacute phase of stroke, as in SO_2S, could be effective, but, given the results so far, this seems unlikely. Indeed, there is increasing concern that high-dose oxygen treatment could be harmful after stroke and in other forms of neurological injury. Hyperoxia ($PaO_2 > 39.99$ kPa) was *independently associated* with mortality in a large retrospective cohort study of ventilated stroke patients.[87] Hyperoxia has also been related to delayed cerebral ischaemia in patients with subarachnoid haemorrhage ($PaO_2 > 23.06$ kPa),[88] to higher mortality and worse functional outcomes in traumatic brain injury ($PaO_2 > 26.66$ kPa),[89] and to increased in-hospital mortality following resuscitation from cardiac arrest ($PaO_2 > 39.99$ kPa).[90] It is therefore highly unlikely that a higher dose of oxygen would have been more effective.

Oxygen treatment may have been ineffective because of poor compliance

Oxygen treatment can be effective only when it is given as prescribed. It is relatively easy to ensure that tablets or injections are given and to check compliance, as all drug treatments are recorded in the drug chart. Oxygen treatment is also prescribed on the drug chart, but given continuously, so that it is not possible to record compliance at all time points. Acute stroke patients are often confused and restless, and intentional or accidental removal of the nasal cannulae or oxygen mask is common. Minor benefits from oxygen treatment might therefore have been masked by poor compliance. Compliance with oxygen treatment was checked by two methods. Investigators were asked to document whether or not trial oxygen was prescribed. This was done as instructed in > 99% patients in the oxygen groups. They were also required to document whether or not the oxygen was actually given. The latter was recorded unreliably in the drug charts. Oxygen is normally prescribed only once as a continuous treatment, and nurses were not used to signing for ongoing oxygen treatment as they would for doses of medicines. To encourage more reliable recording of administration, we instructed centres to circle time points for signatures in the drug chart and put marks onto each field/time point requiring a signature (four times daily). In addition, we amended the protocol to require spot checks of compliance with oxygen treatment at different time points (00:00 and 06:00). This applied to the final 4144 patients. The results showed that oxygen was administered as prescribed in 65–83% of participants. These spot checks also showed that 3% of the control patients had oxygen in place at midnight and 6 a.m. Prescription of oxygen for clinical indications was permitted in all three treatment groups, and it was therefore appropriate that a small proportion of patients in the control group were found to have oxygen in place. While the main analysis of the study was intention to treat, a sensitivity analysis was conducted to examine the effects of non-compliance. This confirmed the main results that oxygen treatment, whether given continuously or at night-time only, did not improve outcome. The OR of the comparison of the combined oxygen groups with the control group was below 1, suggesting a possibility of harm, rather than benefit. However, this effect was very small and not significant statistically. It does nevertheless make poor compliance a less likely reason for ineffectiveness. Furthermore, oxygen treatment increased oxygen saturation in both the continuous and the night-time only treatment groups. Despite suboptimal compliance, we found highly

significant increases of 0.8% and 0.9% in the highest and lowest oxygen saturations, respectively, in the oxygen groups compared with the control group during the intervention. While these changes in saturation are small, because of the S-shape of the haemoglobin dissociation curve, even small changes in oxygen saturation can reflect significant differences in the amount of oxygen dissolved in the blood. The high mean baseline oxygen saturation (96.6%) placed many participants on the flat part of the curve, where saturation changes little with increasing blood oxygen concentrations. A dose-ranging study of oxygen supplementation in stroke patients showed a 2.2% increase in oxygen saturation with 2 l/minute and a 2.9% increase with 3 l/minute.[31] In this study patients were observed continuously so that non-compliance could be excluded. However, the baseline oxygen saturation was lower at 95% and this will also have contributed to the relatively larger response. SO_2S was a pragmatic study and aimed to reflect clinical practice rather than strictly supervised experimental conditions. Better compliance would require continuous observation of patients, and this is impracticable outside an intensive care unit.

Few participants in the Stroke Oxygen Study were recorded as being hypoxic

When planning the study we may have overestimated the number of patients who develop hypoxia. If hypoxia is uncommon, the effect of prophylactic treatment would be diluted. In SO_2S very few (1.8%) participants in either group were recorded as having oxygen desaturations below 90%, with no differences between groups. In the Stroke Oxygen Pilot Study, 20% of patients in the oxygen group and 33% in the control group spent > 5 minutes with an oxygen saturation below 90% at night, but only 4% and 5%, respectively, spent > 60 minutes with an oxygen saturation below 90%.[31] Age, baseline oxygen saturation and NIHSS scores were similar in both studies. In the pilot study, oxygen desaturation was recorded continuously by pulse oximetry, while in SO_2S pulse oximetry readings were taken from intermittent measurements recorded in the patients' notes. It is likely that short episodes of hypoxia were missed in SO_2S. This fits with evidence from a meta-analysis of continuous compared with intermittent monitoring of stroke patients, which also shows that intermittent monitoring detects fewer episodes of hypoxia than continuous monitoring.[91] A study of patients recovering from non-cardiac surgery showed that intermittent monitoring by ward nurses in a non-intensive care setting missed 90% of hypoxaemic episodes in which saturation was < 90% for at least 1 hour.[92] It is reasonable to assume that intermittent monitoring on stroke units is no more effective than that.

Neither the Stroke Oxygen Pilot Study nor SO_2S found a significant difference in severe desaturations between the treatment and control groups, which may indicate that low-dose oxygen supplementation is not sufficient to prevent severe desaturations.[31] Intermittent spot checks of oxygen saturation are likely to miss a significant number of transient episodes of hypoxia. This study was not designed to monitor oxygen saturation. It is unlikely that the Stroke Oxygen Study population has had fewer episodes of hypoxia than other stroke populations monitored continuously. It is therefore very unlikely that the lack of effect can be explained by rarity of hypoxic episodes.

Oxygen may have been started too late to have an effect

In SO_2S oxygen treatment was started at a median of 20 hours 43 minutes after symptom onset. This is well after the hyperacute phase of the stroke. It is therefore not possible to determine from the results of this study whether or not earlier oxygen treatment might have been more effective. However, other studies of oxygen treatment after stroke have enrolled patients earlier (Rønning and Guldvog[29] within 24 hours, Singhal *et al.*[30] and Singhal 2010[86] within 8 hours, and Chiu *et al.*[93] within 12 hours), but also showed no beneficial effect.

Oxygen might still be beneficial, if given to the right subgroup of patients

Subgroup analyses did not identify any class of patient that was more likely to benefit from oxygen treatment. This included patients enrolled soon after onset of stroke, those with lower baseline oxygen saturation and patients with more severe strokes, the groups that were expected to be most likely to benefit from oxygen. However, patients who clearly needed oxygen because of dyspnoea or hypoxia were not enrolled into the study. The results of SO_2S can therefore not be extrapolated to this subgroup.

Incomplete blinding may have introduced bias

Patients tend to expect benefit from active treatment rather than from control. For oxygen, this may apply more than for unknown new interventions, as many patients know that the brain needs oxygen and that oxygen cannot get to the brain when the blood supply is blocked. Giving more thus makes sense intuitively. Knowing whether or not they have had oxygen could thus have affected their assessment of recovery. Just under 50% of participants remembered their treatment allocation correctly at 3 months, reducing with time to 35% at 12 months. Bias towards effectiveness of oxygen treatment cannot be excluded with an open design. Bias towards assuming a worse outcome with oxygen treatment is very unlikely. SO_2S did not show any effect of active treatment on any of the outcomes. While strong positive bias of the patients could have masked an adverse effect, this is unlikely. In addition, the lack of effect on functional outcomes was mirrored by a lack of effect on mortality, and the latter is not subject to bias.

Limitations to the study

Our aim was to test whether or not ROS improves outcome, not whether or not treating manifest hypoxia is beneficial. We have not included patients who were severely hypoxic (oxygen saturation below 90%) or had other definite indications for oxygen in the study. Therefore the results of the study do not apply to patients with severe hypoxia or those with definite indications for oxygen treatment not related to the stroke.

What does the Stroke Oxygen Study add to existing evidence?

There are two other published studies of low-dose oxygen supplementation after acute stroke.[30,85] In contrast to the much smaller Stroke Oxygen Pilot Study,[31] we found no evidence of better early neurological recovery with oxygen. Our results confirm the findings of Rønning and Guldvog,[29] who conducted a much smaller study, and found no overall benefit from oxygen given at 3 l/minute for 24 hours. While their subgroup analysis suggested a possibility of harm from oxygen in mild strokes, we found no evidence of an adverse effect on outcome in the subgroup of patients with mild strokes or with TIAs. While our results do not support routine oxygen treatment, they do provide reassurance on its safety.

A search of the literature identifying all randomised controlled studies investigating the effect of routine normobaric oxygen treatment on functional or neurological outcome in patients with acute stroke using a series of terms including ‘stroke’, ‘oxygen’ and ‘clinical trial’ up to March 2015 identified four published studies[29–32,85] and one study reporting results online only.[86] A total of 979 patients were included. Oxygen was given in doses ranging from 2 to 45 l/minute and for durations of 8–72 hours. A meta-analysis was conducted including these and 8003 patients enrolled into SO_2S. Statistical heterogeneity for these studies was moderate ($I^2 = 31\%$; Cochran Q; $p = 0.21$) and study estimates were combined using a Mantel–Haenszel method in a random-effects model. There was no reduction in mortality at 90 days (or by the end of follow-up when 90-day outcomes were not available) with oxygen treatment, with an averaged OR across studies of 1.11 (95% CI 0.84 to 1.46). Oxygen also had no effect on recovery, when reported (five out of six studies). SO_2S provides clear evidence and adequate power to establish that ROS early after acute stroke does not improve outcome. As SO_2S is much larger than earlier trials, the results of the meta-analysis reflect the outcome of this study. There is no indication from the other studies that giving oxygen earlier is more beneficial, or that higher doses are more effective. Unpublished results from one small study suggest that very high doses of oxygen may be associated with higher mortality (Aneesh B Singhal, Massachusetts General Hospital, 2010, personal communication). Concern about the potential of excessive doses of oxygen to cause harm has also been raised by a non-randomised observational study of 2894 ventilated stroke patients treated on intensive care units, for which hyperoxia was associated with higher mortality than both hypoxia and normoxia.[87]

Rapid recruitment and study set-up

The Stroke Oxygen Study is the largest and fastest recruiting stroke study enrolling patients from the UK only. Recruitment of trial sites and set-up was facilitated by the stroke research network. This study would not have been possible without the research staff and infrastructure provided by the network.

Health economics

The results of the health economics analysis are in line with the clinical findings, demonstrating that there is no benefit from offering patients oxygen supplementation in hospital after stroke. The treatment does not result in significantly higher quality-adjusted survival and neither does it mean that patients return home more quickly, but it does increase costs of treatment. The point estimates of cost-effectiveness and the results shown in the CEACs do not suggest that the treatment is cost-effective. When the analysis considered all three trial treatments, nocturnal ROS was dominated, that is associated with slightly poorer outcomes but higher costs than no ROS. Continuous ROS resulted in about 3.5 days of home time gained, but this did not translate into significant QALY gains and the ICER was still well above the £20,000 to £30,000 NICE willingness-to-pay threshold used by UK NHS decision-makers. The CEAC also demonstrated a low probability of cost-effectiveness (31%) at £20,000/QALY. Implications for practice are that it should be recommended that patients do not need to receive oxygen supplementation unless clinically indicated.

This is the first health economics analysis of ROS compared with no ROS in stroke patients, and compared with many other economic evaluations has a very large sample size, thus increasing confidence in the robustness of the results. The main limitations of this study relate to data collection. In the majority of trial-based analyses it is possible to collect baseline quality-of-life data, which are then used in the calculation of QALYs. However, this data collection is not possible in acute admission for stroke. This creates problems in calculating QALYs; therefore, assumptions have to be made about the baseline quality of life. This issue has been explored previously and the methodology has been repeated here: the baseline quality of life score is assumed to be zero and then quality of life increases linearly to the 3-month score.[79] Obviously, patient quality of life trajectories will vary considerably, with some patients recovering very quickly, thus underestimating QALYs in the first 3 months. An alternative method was used in the analysis, with the 3-month score also being used for the baseline score. Comparison of the results of the two methods showed that there was no overall impact on the direction of the results. This remains an area in which further research is needed on the optimum way of dealing with baseline quality of life where data collection is not possible.

Detailed data were also not available on patients with regard to date of discharge and destination, or readmissions. Completion of parts of the patient questionnaires was suboptimal, and data collection on such a large number of patients also presented logistical difficulties. Therefore, assumptions were required regarding final discharge destination and an average length of readmission was assumed and an overall average cost applied, which may result in reducing the overall variability of health-care costs. Finally, the costs used for long-term care post discharge were obtained from a report from 2002.[79] More up-to-date costs of care for independent and dependent patients were sought; however, scrutiny of the literature did not yield any costs that were appropriate for this analysis and many economic evaluations in stroke since 2002 have used the same unit costs.

Future work

Post-stroke hypoxia is associated with adverse outcomes after stroke. SO_2S has shown that routine low-dose oxygen supplementation does not improve this. Subgroup analysis has not identified any patient group more likely to benefit. We cannot exclude that very early enrolment could make a difference, but this was not supported by results from the small subgroup enrolled within less than 6 hours. We cannot extrapolate

our results to use of high doses of oxygen, but there is currently no good support from published studies in humans. Evidence from observational studies suggests that hypoxia, especially if untreated, is associated with adverse outcomes. Hypoxia is a sign of underlying pathology (e.g. airway obstruction, pneumonia, heart failure, pulmonary embolism), which requires specific treatment. It is possible that oxygen treatment delays recognition and thereby also treatment of these complications. Future work should therefore focus on early detection and/or prevention of hypoxia.

The nature of the trial and large sample size will allow further analyses to be undertaken in the future to explore important questions regarding outcomes in the first 12 months after stroke. Two further analyses are planned. First, mean EQ-5D-3L scores will be calculated for groupings of mRS score levels to represent independence and dependence after stroke. These data will be valuable for use by future decision models for stroke, allowing the use of patient-reported utility values for model health states. The validity and the responsiveness of the EQ-5D-3L questionnaire in stroke patients will be explored by comparing responses with patient scores for the mRS, BI and the NEADL.

Conclusions

In conclusion, the results of SO_2S conclusively demonstrate that low-dose oxygen supplementation in patients who are not severely hypoxic increases oxygen saturation, but is not associated with benefits after acute stroke in the whole population or in any of the subgroups. The observed lack of benefit is consistent across all outcomes and all time points up to 1 year, and the same whether oxygen is given continuously or at night-time only. Results of the health economic analysis confirm the lack of benefit of oxygen in quality of life and economic terms. Future research should address causes of hypoxia and examine methods to prevent the development of hypoxia.

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Contributions of authors

Christine Roffe originated the study idea, has been chief investigator for the trial and has drafted this report.

Tracy Nevatte was the trial manager and made major contributions to the draft report.

Jon Bishop did the statistical analysis.

Julius Sim contributed to the statistical analysis, conducted the sensitivity analyses and critically revised the manuscript.

Cristina Penaloza and **Susan Jowett** wrote the health economic section of the report.

Natalie Ives contributed to the protocol paper and the statistical analysis plan, and the interpretation of the results.

Richard Gray contributed to the development of the protocol and statistical analysis plan and the interpretation of the results.

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Data sharing statement

We will make all data (with the exception of personally identifiable data) available to the scientific community once the key outputs have been published.

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Appendix 1 Participating hospitals and Stroke Oxygen Study collaborators

Patients were recruited to the SO_2S from 136 hospitals across the UK. Hospitals, local principal investigators, and numbers recruited per centre are listed according to the number enrolled starting with the highest recruiting centre.

1. University Hospital of North Staffordshire (C Roffe) (478)
2. St George's Hospital (B Moynihan) (288)
3. The Royal Liverpool University Hospital (A Manoj) (256)
4. Royal Bournemouth General Hospital (D Jenkinson) (240)
5. Kings College Hospital (L Kalra) (231)
6. Leeds General Infirmary (P Wanklyn) (204)
7. Salford Royal Hospital (C Smith) (191)
8. Southend Hospital (P Guyler) (188)
9. Countess Of Chester Hospital (K Chatterjee) (176)
10. The Royal Victoria Infirmary (A Dixit) (168)
11. Royal Sussex County Hospital (K Ali) (164)
12. Musgrove Park Hospital (M Hussain) (156)
13. Wansbeck Hospital (C Price) (155)
14. Bristol Royal Infirmary (P Murphy) (151)
15. Royal Preston Hospital (S Punekar) (149)
16. University Hospital Aintree (R Durairaj) (148)
17. Birmingham Heartlands Hospital (D Sandler) (143)
18. Pennine Acute (Rochdale) (R Namushi) (134)
19. Queen's Hospital, Burton (B Mukherjee) (131)
20. University Hospital Coventry (Walsgrave) (P Kanti – Ray) (129)
21. Royal Devon & Exeter Hospital (Wonford) (M James) (113)
22. Royal United Hospital Bath (L Shaw) (113)
23. Royal Cornwall Hospital (Treliske) (F Harrington) (112)
24. Queen Elizabeth The Queen Mother Hospital (G Gunathilagan) (105)
25. York Hospital (J Coyle) (105)
26. University Hospital Of North Durham (B Esisi) (99)
27. Derriford Hospital (A Mohd Nor) (95)
28. Selly Oak Hospital (Acute) (D Sims) (92)
29. St Helen's & Knowsley Hospitals Trust (V Gowda) (89)
30. Torbay District General Hospital (D Kelly) (88)
31. Charing Cross Hospital (P Sharma) (87)
32. Leighton Hospital (M Salehin) (87)
33. Kent & Canterbury Hospital (I Burger) (84)
34. New Cross Hospital (K Fotherby) (84)
35. Northwick Park Hospital (D Cohen) (83)
36. Barnsley District General Hospital (M Albazzaz) (82)
37. Blackpool Victoria Hospital (J Mcilmoyle) (82)
38. Princess Royal University Hospital (L Sztriha) (81)
39. Eastbourne District General Hospital (C Athulathmudali) (76)
40. Warrington Hospital (K Mahawish) (75)
41. City Hospitals Sunderland (N Majmudar) (69)
42. William Harvey Hospital (Ashford) (D Hargroves) (69)
43. Stepping Hill Hospital (A Krishnamoorthy) (66)
44. The James Cook University Hospital (D Broughton) (66)

45. Northampton General Hospital (Acute) (M Blake) (59)
46. Leicester General Hospital (A Mistri) (57)
47. Rotherham District General Hospital (J Okwera) (56)
48. St Peter's Hospital (R Nari) (56)
49. Macclesfield District General Hospital (M Sein) (55)
50. Manor Hospital (K Javaid) (54)
51. Bradford Royal Infirmary (C Patterson) (53)
52. Luton & Dunstable Hospital (L Sekaran) (50)
53. Royal Blackburn Hospital (N Goorah) (50)
54. University College Hospital (R Simister) (50)
55. North Tyneside General Hospital (C Price) (48)
56. Addenbrooke's Hospital (E Warburton) (48)
57. Queen Alexandra Hospital (D Jarrett) (47)
58. North Devon District Hospital (M Dent) (45)
59. Pilgrim Hospital (D Mangion) (44)
60. Solihull Hospital (K Elfandi) (44)
61. Norfolk & Norwich University Hospital (N Shinh) (41)
62. Gloucestershire Royal Hospital (D Dutta) (40)
63. Royal Surrey County Hospital (A Blight) (39)
64. Southport & Formby District General Hospital (P McDonald) (39)
65. Bishop Auckland General Hospital (A Mehrzad) (35)
66. Airedale General Hospital (E AdbusSammi) (34)
67. Calderdale Royal Hospital (P Rana) (34)
68. Doncaster Royal Infirmary (D Chadha) (34)
69. East Surrey Hospital (B Mearns) (34)
70. Medway Maritime Hospital (S Sanmuganathan) (34)
71. Royal Derby Hospital (T England) (33)
72. Wycombe General Hospital (M Burn) (33)
73. Princess Royal Hospital (R Campbell) (32)
74. Harrogate District Hospital (S Brotheridge) (30)
75. Peterborough City Hospital (P Owusu-Agyei) (30)
76. West Cumberland Hospital (O Orugun) (30)
77. Colchester General Hospital (R Saksena) (29)
78. Royal Hampshire County Hospital (N Smyth) (29)
79. Dorset County Hospital (H Prosche) (27)
80. Frimley Park Hospital (B Clarke) (27)
81. Royal Hallamshire Hospital (M Randall) (27)
82. Yeovil District Hospital (K Rashed) (25)
83. Poole General Hospital (S Ragab) (24)
84. Frenchay Hospital (N Baldwin) (22)
85. Princess Alexandra Hospital (S Hameed) (22)
86. West Suffolk Hospital (A Azim) (22)
87. The Ulster Hospital (M Power) (21)
88. Watford General Hospital (D Collas) (21)
89. Southampton General Hospital (N Weir) (20)
90. Craigavon Area Hospital (M McCormick) (19)
91. Royal Lancaster Infirmary (P Kumar) (18)
92. Basildon Hospital (R Rangasamy) (17)
93. City Hospital Birmingham (S Kausar) (17)
94. Nottingham University Hospitals (A Shetty) (16)
95. Antrim Area Hospital (J Vahidassr) (15)
96. Pinderfields General Hospital (P Datta) (15)
97. Royal Albert Edward Infirmary (S Herath) (15)

98. Good Hope Hospital (E Smith) (14)
99. Hereford County Hospital (C Jenkins) (13)
100. South Tyneside District General Hospital (J Scott) (13)
101. Broomfield Hospital (V Umachandran) (12)
102. Wythenshawe Hospital (E Gamble) (11)
103. Warwick Hospital (B Thanvi) (10)
104. Ipswich Hospital (J Ngeh) (9)
105. Kettering General Hospital (K Ayres) (9)
106. Nevill Hall Hospital (B Richard) (9)
107. Scarborough General Hospital (J Paterson) (9)
108. Hull Royal Infirmary (A Abdul-Hamid) (8)
109. King's Mill Hospital (M Cooper) (8)
110. The Royal London Hospital (P Gompertz) (8)
111. Trafford General Hospital (S Musgrave) (8)
112. Altnagelvin Area Hospital (J Corrigan) (7)
113. Darent Valley Hospital (P Aghoram) (7)
114. Royal Berkshire Hospital (A Van Wyk) (6)
115. Arrowe Park Hospital (R Davies) (5)
116. Basingstoke and North Hampshire Hospital (E Giallombardo) (5)
117. Lincoln County Hospital (S Leach) (5)
118. Hexham General Hospital (C Price) (4)
119. Manchester Royal Infirmary (J Simpson) (4)
120. Salisbury District Hospital (T Black) (4)
121. Mayday University Hospital (E Lawrence) (3)
122. Russells Hall Hospital (A Banerjee) (3)
123. Worthing Hospital (S Ivatts) (3)
124. Bedford Hospital (A Elmarimi) (2)
125. James Paget Hospital (M Zaidi) (2)
126. St Richard's Hospital (S Ivatts) (2)
127. Erne Hospital (J Kelly) (1)
128. University Hospital Lewisham (M Patel) (1)
129. Bronglais General Hospital (P Jones) (0)
130. Hillingdon Hospital (A Parry) (0)
131. Kingston Hospital (L Choy) (0)
132. Morriston Hospital (M Wani) (0)
133. North Middlesex Hospital (R Luder) (0)
134. St Helier Hospital (V Jones) (0)
135. Staffordshire General Hospital (A Oke) (0)
136. The Princess Royal Hospital (K Ali) (0)

Appendix 2 The case report form

Identification sticker or Name Sex male / female DOB DD MON YYYY Unit No /Hiss No	**Stroke Oxygen Study** **Randomisation Form** Trial Centre name Investigator name

STEP 1 ELIGIBILITY FOR TRIAL INCLUSION

Time since admission with a clinical diagnosis of stroke (WHO criteria) less than 24h	YES	NO
Time since stroke onset less than 48 h	YES	NO
Expected to die within 1 year from a non-stroke related illness	YES	NO
Definite indication for continuous oxygen treatment	YES	NO
Definite contraindication to continuous oxygen treatment	YES	NO

Please proceed to patient details if all answers are in the shaded boxes.

STEP 2 PATIENT DETAILS

Date and time of stroke onset (24 h clock) dd-mon-yyyy hh:mm

Oxygen given in the ambulance no / not known / yes

(for yes specify: 24% mask / 28% mask / 35% mask / 40% >40% mask / 2L/min via nasal cannula / 3L/min via nasal cannula / 4 L/min via nasal cannula/ >4l/min via nasal cannula)

Oxygen given after arrival in hospital no / not known / yes

(for yes specify: 24% mask / 28% mask / 35% mask / 40% >40% mask / 2L/min via nasal cannula / 3L/min via nasal cannula / 4 L/min via nasal cannula/ >4l/min via nasal cannula)

Medical History

Chronic obstructive airways disease or asthma [by history or from list of drugs]	YES	NO
Other chronic lung problem [e.g. kyphoscoliosis, thoracoplasty, pneumoconiosis]	YES	NO
Heart failure [by history, exam or >20 mg furosemide or equivalent per day]	YES	NO
Ischaemic heart disease [history of angina or MI or treatment with nitrates or nicorandil]	YES	NO
Atrial fibrillation	YES	NO

Glasgow Coma Scale (please circle one response in each row)

Eye opening	None (1)	To pain (2)	To speech (3)	Spontaneous (4)		
Motor Response	None (1)	Extension (2)	Abnormal flexion (3)	Withdrawal (4)	Localizes to pain (5)	Obeys commands (6)
Verbal resp.	None (1)	Incomprehensible (2)	Inappropriate (3)	Confused (4)	Oriented (5)	

STEP 3 PROGNOSTIC FACTORS (please circle the yes or no and complete oxygen saturation)

1.1 Age (no need to enter here, will be calculated from DOB and date of stroke)		
1.2 Living alone before the stroke	YES	NO
1.3 Independent in activities of daily living before the stroke	YES	NO
1.4 Normal verbal response to questions (e.g. verbal Glasgow coma Scale Score=5)	YES	NO
1.5 Able to lift the affected arm against gravity	YES	NO
1.6 Able to walk unaided	YES	NO
2. Oxygen treatment prior to randomisation (ambulance or emergency department)	YES	NO
3. Oxygen saturation on room air at randomisation	____ %	
4. Blood glucose (result of BM stick suffices)	____ mmol/l or _____ g/dl	

STEP 4 NIH Stroke Scale

1a Level of Consciousness **(LOC)**	0	Alert – *keenly responsive*
	1	Drowsy – *arousable by minor stimulation to obey, answer, or respond*
	2	Stuporous – *requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped)*
	3	**Comatose** – *responds only with reflex motor or autonomic effects or totally unresponsive, flaccid*
1b LOC Questions	0	Answers both correctly
	1	Answers one correctly
	2	Both incorrect **or no reply**
		Patient is asked to state the month & his/her age
1c LOC Commands	0	Obeys both correctly
	1	Obeys one correctly
	2	Both incorrect **or no reply**
		Patient is asked to open & close eyes, grip & release normal hand
2. Best Gaze	0	Normal
	1	Partial gaze palsy – *gaze is abnormal in one or both eyes, no forced deviation/total gaze paresis*
	2	Forced deviation – *or total gaze paresis not overcome by oculocephalic maneouvre*
3. Visual Fields	0	No visual loss (**or in coma**)
	1	Partial hemianopia
	2	Complete hemianopia
	3	Bilateral Hemianopia – *including cortical blindness*
4. Facial Palsy	0	Normal
	1	Minor - *flattened nasolabial fold, asymmetry on smiling*
	2	Partial – *total or near total paralysis of lower face*
	3	Complete - *absent facial movement in upper and lower face on one or both sides*

5/6 Best Motor ARM	Right	Left	
	0	0	No drift – *holds limb at 90 degrees for full 10 seconds*
	1	1	Drift - *drifts down but does not hit bed*
	2	2	Some effort against gravity
	3	3	No effort against gravity
	4	4	No movement

7/8. Best Motor LEG	Right	Left	
	0	0	No drift – *holds limb at 45 degrees for full 5 seconds*
	1	1	Drift - *drifts down but does not hit bed*
	2	2	Some effort against gravity
	3	3	No effort against gravity
	4	4	No movement

9. Limb Ataxia	0	Absent **(or in coma)**
	1	Present in 1 limb
	2	Present in 2 or more limbs
10. Sensory	0	Normal
	1	Partial loss – *patient feels pinprick is less sharp or is dull on affected side*
	2	Dense loss (**or in coma)** - *patient is unaware of being touched on face, arm, leg*
11. Best Language	0	No dysphasia
	1	Mild – moderate dysphasia *obvious loss of fluency or comprehension, without significant limitation on ideas expressed or form of expression. Makes conversation about provided material difficult or impossible, e.g. examiner can identify picture or naming card from patient's response.*
	2	Severe dysphasia - *all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener who carries burden of communication. Examiner cannot identify materials provided from patient response*
	3	Mute *no usable speech or auditory comprehension,* **or in coma**.
12. Dysarthria	0	Normal articulation
	1	Mild – moderate dysarthria - *patient slurs some words, can be understood with some difficulty.*
	2	Unintelligible or worse - *speech is so slurred as to be unintelligible (absence of or out of proportion to dysphasia) or is mute/anarthric,* **or in coma**
13. Neglect	0	No neglect **(or in coma)**
	1	Partial neglect - *Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities*
	2	Complete neglect - *Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognise own hand or orients to only one side of space*
Total:		

STEP 5 CONTACT likely or preferred location for week 1 follow-up

☐Clinic
☐Home
☐Hospital same as randomizing centre
☐Hospital different to randomizing centre – please give name
☐Other _____

STEP 6 CONSENT

1. Fully informed consent	YES	NO
2. Patient does not disagree with trial	YES	NO
3. Consent from next of kin	YES	NO

Before randomisation either 1 ***OR*** 2 **and** 3 must be answered as **YES**

STEP 7 RANDOMISATION via http://www.so2s.co.uk or [redacted] (day) or [redacted] (after hours)

Date and time of randomisation ☐ dd-mon-yyyy ☐ hh:mm (24 h clock)
Randomisation number ☐ Print Name _____ Sign and Date

Monitor oxygen saturation 30 minutes after the start of treatment and 6 hourly thereafter.

Stroke Oxygen Study Week 1 (Assessment form)

Name _____ Randomisation no _____
Home address:_____

Home telephone no: _____ NHS number _____

Has the patient died? yes / no Date of death _____ DD MON YYYY
Please complete the Notification of Death Form (form 3) if the patient is deceased.

Has the patient had serious adverse events? If yes, please complete SAE form (form 4) yes / no

Oxygen administration for clinical indications during the 72 hour trial period:

☐ The patient was prescribed or received continuous oxygen for clinical indications
☐ The patient was not prescribed or given continuous oxygen for clinical reasons outside the trial treatment

Compliance with oxygen treatment as prescribed for this study:

☐ Oxygen prescribed for 3 nights and signed in the drug chart as instructed
☐ Oxygen prescribed for 3 nights, but not signed as instructed (please explain_____)
☐ Oxygen prescribed for 72 hours and signed as instructed
☐ Oxygen prescribed for 72 hours and not signed as instructed (please explain_____)
☐ Oxygen stopped before the end of 3 days/nights (give reason)
Reason for not completing prescribed oxygen treatment_____
☐ Patient is on the control group (no trial oxygen prescribed)

Clinical data during the first week after trial inclusion:

Antibiotics prescribed after randomization	YES	NO
Thrombolysis performed	YES	NO
Sedatives or antipsychotic drugs prescribed after randomizaton	YES	NO
Highest temperature during week 1		

Other clinical trials:

Has the patient been enrolled in any other clinical trials? YES / NO
If yes, please specify give name of trial:

Record of oxygen saturation and treatment during the first 3 days
Please check compliance with treatment daily and make sure night staff is aware of the study and assessments if saturation or oxygen treatment has not been documented as instructed.

Day 1	
Oxygen saturation at 24:00 (midnight) night 1	
Oxygen is in place at 24:00	YES / NO
Oxygen saturation at 6 am night 1	
Oxygen is in place at 06:00	YES / NO
Day 2	
Oxygen saturation at 12:00 (lunchtime) day 2	
Oxygen saturation at 24:00 (midnight) night 2	
Oxygen is in place at 24:00	YES / NO
Oxygen saturation at 6 am night 2	
Oxygen is in place at 06:00	YES / NO
Day 3	
Oxygen saturation at 12:00 (lunchtime) day 3	
Oxygen saturation at 24:00(midnight) night 3	
Oxygen is in place at 24:00	YES / NO
Oxygen saturation at 6 am night 3	
Oxygen is in place at 06:00	YES / NO

The highest oxygen saturation during the 3 days of trial treatment	
The lowest oxygen saturation during the 3 days of trial treatment	
The highest heart rate during the 3 days of trial treatment	
The highest systolic blood pressure during the 3 days of trial treatment	
The highest diastolic blood pressure during the 3 days of trial treatment	

CT /MRI diagnosis (please tick one of the boxes)
☐ Cerebral infarct
☐ Primary intracerebral haemorrhage
☐ Subdural haemorrhage
☐ Subarachnoid haemorrhage
☐ Brain tumour
☐ Head scan not performed
☐ Other (please specify) _____

Second CT head scan (if performed) date (dd-mon-yyyy)_____ New haemorrhage Yes / no

Final diagnosis (Please make a final diagnosis using the clinical presentation, time course, head scan. Tick only one of the boxes)

☐ Ischaemic stroke
☐ TIA
☐ Primary intracerebral haemorrhage
☐ Cerebrovascular accident without CT confirmation of aetiology
☐ Other (Please specify) _____

Date of discharge …….. (DD-MON-YYYY)

If this is not available at the day 7 follow-up please complete once patient has been discharged.

Discharge location (*If this is not available at the day 7 follow-up please complete once patient has been discharged):*

☐ Patients own home
☐ Home of a relative
☐ Residential home
☐ Nursing home
☐ Another hospital – please provide name ……..
☐ Other ……..

Pre-Stroke Rankin

This is to be completed by the researcher with the either the patient, a relative or carer in relation to how the patient was before the stroke (i.e. based on the day before the stroke).

☐ No symptoms at all
☐ Few symptoms, but able to carry out usual activities as normal
☐ Unable to carry out all usual activates, but can look after own affairs without assistance
☐ Need some help with looking after own affairs, but can walk without assistance
☐ Unable to walk or attend bodily needs without assistance, but constant care not needed
☐ Major symptoms that severely handicap. Bedridden, incontinent and require constant attention day and night

Completed by:

☐ Patient
☐ Other, please specify _____

Pre-stroke EQ – 5D

This is to be completed by the researcher with the either the patient, a relative or carer in relation to how the patient was before the stroke (i.e. based on the day before the stroke).

Mobility - Please tick the box which best describes the patients level of mobility before the stroke

☐ I had no problems walking
☐ I had some problems walking
☐ I was confined to bed

Self care - Please tick the box which best describes the patients ability to care for themselves before the stroke

☐ I had no problems with self care
☐ I had some problems washing and dressing
☐ I was unable to wash or dress myself

Usual activities - Please tick one box next to the statement which best describes their ability to perform their usual activities before the stroke

☐ I was able to perform my usual activities
☐ I has some problems performing my usual activities
☐ I was unable to perform my usual activities

Pain or discomfort - Please tick one box next to the statement which best describes their level of pain or discomfort before the stroke

☐ I had no pain or discomfort
☐ I had moderate pain or discomfort
☐ I had extreme pain or discomfort

Anxiety and depression - Please tick one box next to the statement which best describes their level of anxiety and depression before the stroke

☐ I was not anxious or depressed
☐ I was moderately anxious or depressed
☐ I was extremely anxious or depressed

Completed by:

☐ Patient

☐ Other, please specify _____

NIH Stroke Scale

1a Level of Consciousness **(LOC)**	0 1 2 3	Alert – *keenly responsive* Drowsy – *arousable by minor stimulation to obey, answer, or respond* Stuporous – *requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped*) **Comatose** – *responds only with reflex motor or autonomic effects or totally unresponsive, flaccid*
1b LOC Questions	0 1 2	Answers both correctly Answers one correctly Both incorrect **or no reply** Patient is asked to state the month & his/her age
1c LOC Commands	0 1 2	Obeys both correctly Obeys one correctly Both incorrect **or no relpy** Patient is asked to open & close eyes, grip & release normal hand
2. Best Gaze	0 1 2	Normal Partial gaze palsy – *gaze is abnormal in one or both eyes, no forced deviation/total gaze paresis* Forced deviation – *or total gaze paresis not overcome by oculocephalic maneouvre*
3. Visual Fields	0 1 2 3	No visual loss **(or in coma)** Partial hemianopia Complete hemianopia Bilateral Hemianopia – *including cortical blindness*
4. Facial Palsy	0 1 2 3	Normal Minor - *flattened nasolabial fold, asymmetry on smiling* Partial – *total or near total paralysis of lower face* Complete - *absent facial movement in upper and lower face on one or both sides*
5/6 Best Motor ARM	Right / Left	
	0 / 0	No drift – *holds limb at 90 degrees for full 10 seconds*
	1 / 1	Drift - *drifts down but does not hit bed*
	2 / 2	Some effort against gravity
	3 / 3	No effort against gravity
	4 / 4	No movement
7/8. Best Motor LEG	Right / Left	
	0 / 0	No drift – *holds limb at 45 degrees for full 5 seconds*
	1 / 1	Drift - *drifts down but does not hit bed*
	2 / 2	Some effort against gravity
	3 / 3	No effort against gravity
	4 / 4	No movement
9. Limb Ataxia	0 1 2	Absent **(or in coma)** Present in 1 limb Present in 2 or more limbs
10. Sensory	0 1 2	Normal Partial loss – *patient feels pinprick is less sharp or is dull on affected side* Dense loss (**or in coma**) - *patient is unaware of being touched on face, arm, leg*
11.Best Language	0 1 2 3	No dysphasia Mild – moderate dysphasia *obvious loss of fluency or comprehension, without significant limitation on ideas expressed or form of expression. Makes conversation about provided material difficult or impossible, e.g. examiner can identify picture or naming card from patient's response.* Severe dysphasia - *all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener who carries burden of communication. Examiner cannot identify materials provided from patient response* Mute *no usable speech or auditory comprehension,* **or in coma**.
12. Dysarthria	0 1 2	Normal articulation Mild – moderate dysarthria - *patient slurs some words, can be understood with some difficulty*. Unintelligible or worse - *speech is so slurred as to be unintelligible (absence of or out of proportion to dysphasia) or is mute/anarthric,* **or in coma**
13. Neglect	0 1 2	No neglect **(or in coma)** Partial neglect - *Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities* Complete neglect - *Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognise own hand or orients to only one side of space*
Total		

TOAST criteria (complete for infarcts only)

☐ **Large-artery atherosclerosis (LAA)**

(tick this if there is Imaging evidence of >50% stenosis of intracranial or extracranial artery)

☐ **Cardioembolism (CE)**

(Evidence of a medium-risk cardiac source of embolism **and** no other cause of stroke)

☐ **Small-artery occlusion (lacunar infarct)**

(Clinically lacunar syndrome **and** lacunar infarct on CT **and** no evidence for ipsilat. LAA or CE)

☐ **Acute ischaemic stroke of other determined aetiology**

(rare causes of stroke, such as nonatherosclerotic vasculopathies, hypercoagulable states, or

haematological disorders **and** no evidence for LAA or CE)

☐ **Ischaemic stroke of undetermined aetiology**

(any patient who does not fit the above, e.g. fully investigated patients with >1 potential cause

of stroke or patients who have not been fully investigated)

Large-artery atherosclerosis (LAA)

These patients will have clinical and brain imaging findings of either significant (>50%) stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis. Clinical findings include those of cerebral cortical impairment (aphasia, neglect, restricted motor involvement, etc.) or brain stem or cerebellar dysfunction. A history of intermittent claudication, transient ischaemic attacks (TIAs) in the same vascular territory, a carotid bruit, or diminished pulses helps support the clinical diagnosis. Cortical or cerebellar lesions and brain stem or subcortical hemispheric infarcts greater than 1.5cm in diameter on CT or MRI are considered to be of potential large-artery atherosclerotic origin. Supportive evidence by duplex imaging or arteriographay of a stenosis of greater than 50% of an appropriate intracranial or extracranial artery is needed. Diagnostic studies should exclude potential sources of cardiogenic embolism. The diagnosis of stroke secondary to large-artery atherosclerosis cannot be made if duplex or arteriographic studies are normal or show only minimal changes.

Cardioembolism (CE)

This category includes patients with arterial occlusions presumably due to an embolus arising in the heart. Cardiac sources are divided into high-risk and medium-risk groups based on the evidence of their relative propensities for embolism. At least one cardiac source for an embolus must be identified for a possible or probable diagnosis of cardioembolism stroke. Clinical and brain imaging finding are similar to those described for large-artery atherosclerosis. Evidence of a previous TIA or stroke in more than one vascular territory or systemic embolism supports a clinical diagnosis of cardiogenic stroke. Potential large-artery atherosclerotic sources of thrombosis or embolism should be eliminated. A stroke

in a patient with a medium-risk cardiac source of embolism and no other cause of stroke is classified as a possible cardioembolic stroke.

Small-artery occlusion (lacunar infarct)

This category includes patients whose strokes are often labelled as lacunar infarcts in other classifications. The patient should have one of the traditional clinical lacunar syndromes and should not have evidence of cerebral cortical dysfunction. A history of diabetes mellitus or hypertension supports the clinical diagnosis. The patient should also have a normal CT/MRI or examination or a relevant brain stem or subcortical hemispheric lesion with a diameter of less than 1.5 cm demonstrated. Potential cardiac sources for embolism should be absent and evaluation of the large extracranial arteries should not demonstrate a stenosis of greater than 50% in an ipsilateral artery.

Acute ischaemic stroke of other determined etiology

This category includes patients with rare causes of stroke, such as nonatherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders. Patients in this group should have clinical and CT or MRI findings of an acute ischaemic stroke, regardless of the size or location. Diagnostic studies such as blood tests or arteriography should reveal one of those unusual causes of stroke. Cardiac sources of embolism and large-artery atherosclerosis should be excluded by other studies.

Ischaemic stroke of undetermined aetiology

In several instances, the cause of a stroke cannot be determined with any degree of confidence. Some patients will have no likely aetiology determined despite an extensive evaluation. In others, no cause is found but the evaluation was cursory. This category also includes patients with two or more potential causes of stroke so that the physician is unable to make a final diagnosis. For example, a patient with a medium-risk cardiac source of embolism who also has another possible cause of stroke identified would be classified as having a stroke of undetermined aetiology. Other examples would be a patient who has atrial fibrillation and an ipsilateral stenosis of 50%, or the patient with a traditional lacunar syndrome and an ipsilateral carotid stenosis of 50%.

Completed by : Print Name _____ Sign and Date

Stroke Oxygen Study
Week 1 (Contact form)

For patients who were incompetent to sign consent at recruitment:

Competent to sign today? ☐Yes ☐No

If yes, explain study again and ask patient to sign patient confirmation of consent (after recovery) form.

Preferred contact address and telephone number for the follow-up questionnaires:

Name:
Street and Number:
Town, County, country:
Postcode:
Tel No:
Mobile no:

Alternative contact address and tel number if preferred address cannot be contacted:

Name:
Street and Number:
Town, County, country:
Postcode:
Tel No:
Mobile no:

Address and telephone number of the patient's general practitioner:

Name of GP:
Street and Number:
Town, County, country:
Postcode:
Tel No:
Fax:

Alternative follow-up arrangements if the patient is unable to complete the 3, 6 or 12 month questionnaire or prefers a personal appointment:

☐ Clinic Appointment
☐ Other

Please complete on line or fax the week 1 assessment form the week 1 contact form and the NIHSS score sheet for randomisation and week 1 to [redacted]

Completed by : Print Name _____ Sign and Date

Stroke Oxygen Study

Notification of Death (Assessment Form 3)

Name ☐ Randomisation number: ☐

Date of Death ☐

Has the cause of death been confirmed by autopsy? Yes ☐ No ☐

Likely cause of death (tick one box only)

☐ Neurological damage due to the initial stroke

☐ Recurrent stroke

☐ Pneumonia

☐ Other infection

☐ Pulmonary Embolism

☐ Ischaemic heart disease

☐ Other cause of death (please specify) _____

Completed by : Print Name _____ Sign and Date

Stroke Oxygen Study
Serious Adverse Event Notification (Assessment Form 4)

Please complete form below and fax to [redacted] and [redacted]
ASAP within 24 hours of becoming aware of the event.

Trial name: The Stroke Oxygen Study
ISRCTN52416964

Report date and time (dd-mon-yyyy hh:mm)
_____
Date of Enrolment _____Adverse Event date and time (dd-mon-yyyy hh:mm)
_____
Centre name
_____Country_____

Randomisation number _____ Age (years) _____ Sex: Male/female

Event information

When did this event happen with regard to the treatment phase?	Before / During / After
Is it a Serious adverse event? An adverse event is defined as serious if any of A-F has been answered with yes. Please describe the event regardless of your answer to A-F. If the answer to questions A-F is 'no' in every case this is not a serious event - Please complete form (R & D-RF-SOS-001)	
A. Did the event result in death?	Yes / No
B. Is / was the event life threatening?	Yes / No
C. Did / does the event lead to hospitalization or prolonged hospitalization?	Yes / No
D. Did / does the event result in persistent or significant disability / incapacity?	Yes / No
E. Did / does the event result in congenital anomaly / birth defect / carcinogenesis?	Yes / No
F. Does the investigator consider the event a serious adverse event for other reasons	Yes / No

A1 Nature of event	Single Multiple Episodes	
Intensity of event / Grading of Serious Adverse Event	Mild Moderate Severe	
A2 Relationship to study drug(s) / Attribution of Serious Adverse Event	Definitely not Unrelated Unlikely	Possibly Probably Definitely Unknown
A3 Action taken regarding study drug(s)	None	Dose(s) missed Discontinued
A4 Clinical outcome	Recovered	Not Yet Recovered Died

B. Please describe the event in detail, providing any relevant medical information. i.e. pathology, radiology, ECG, bacteriology, biochemistry or clinical reports / information.
If the patient has been re-admitted to hospital please provide re-admission date, discharge date and length of stay (days)

C. Assessment of event by local Investigator	
C1. SAE category as adjudicated by local investigator (see attached SAE event categories for guidance)	
C2. Do you consider this SAE unexpected i.e. a Suspected Unexpected Serious Adverse Reaction (SUSAR)?	Yes / No
Form submission sign off - Enter your NAME:	
Date SAE Reported	
Time (24 hour clock) SAE Reported	
Have you checked that all entries above are correct?	Yes / No

D. Assessment by the Chief Investigator	
Is this event considered an SAE by the Chief investigator or deputy?	Yes / No
Is this event considered to be a SUSAR by the Chief investigator /deputy?	Yes / No
If the answer to SUSAR is yes, do you want to send the report to MHRA/ COREC now	
Confirmation of date (dd-mm-yyyy) sent to MHRA/COREC	
Confirmation of time [24 hour clock] sent to MHRA/COREC	
Signature of Chief investigator:	
Follow-up report required	Yes / No
Notes	

AE / SAE Event Categories v1.0

To be used with SAE form v1 amendment 2 (30. Aug.1009)

Cardiovascular
Acute coronary syndrome (ACS)
Atrial fibrillation (AF)
Bradycardia
Cardiac failure
Cardiac dysrhythmia
Chest pain
Collapse
Deep vein thrombosis (DVT)
Hypertension
Hypotension
Myocardial infarction (MI)
Pulmonary embolism (PE)
Tachycardia
Unstable angina

Central nervous system
Agitation
Anxiety
Cerebral oedema
Complication of initial stroke
Dementia
Depression
Dysphagia
Extension of initial stroke
Haemorrhagic transformation (of infarct, HTI)
Headache
Intracerebral bleed
Intracranial/extracerebral bleed
Recurrent stroke
Sedation
Seizure
Sensory loss
Transient ischaemic attack (TIA)
Vertigo
Visual loss
Weakness

Cutaneous
Flushing
Hypersensitivity inc. oropharangeal swelling, urticaria
Rash

Gastro-intestinal
Abdominal pain
Constipation
Diarrhoea
Dysphagia
Gastrointestinal bleed
Gastrointestinal disturbance
Incontinence, faecal
Heartburn
Hepatitis
Nausea
Oral ulceration
Pancreatitis
Vomiting
Weight loss

Genito-urinary
Sexual dysfunction
Incontinence, urinary
Renal impairment
Urinary retention
Urinary tract infection (UTI)

Haematological
Anaemia
Leukopenia
Methaemoglobinaemia
Thrombocytopenia

Immunological
Anaphalactoid reaction
Hypersensitivity

Miscellaneous
Acid base disturbance
Bacteraemia
Death unattended
Diaphoresis
Hyponatraemia
Hypernatraemia
Acidosis
Extracranial bleeding (not GI haemorrhage)
Fall
Fatigue
Hyperglycaemia
Hyperuricaemia
Infection (not otherwise specified)
Malignancy
Muscle twitching
Vascular event (not otherwise specified)

Respiratory
Asthma
Bronchospasm
Chest infection
Hypoxia
Pneumonia
Pulmonary embolism (PE)
Shortness of breath

Oxygen-related
Respiratory depression
Drying of mucous membranes

Other (specify)
_____

Appendix 3 The health economic questionnaire

USE OF RESOURCES QUESTIONNAIRE
(to be completed by a hospital representative)

1. For the use of routine oxygen supplementation (ROS) for a stroke patient in the first 72 hours, what types and grades of staff are required and what is the average **additional** time required per member of staff (over and above all other standard care for the patient)?

Use of staff in ROS per treatment group			
Staff member (title)	Grade	Total time (**in minutes**) allocated per intervention	
		Treatment group 2 Night-time ROS for 72 hours	Treatment group 3 Continuous ROS for 72 hours

2. Please give information on the **additional** equipment required per patient to administer routine oxygen supplementation (ROS) for a stroke patient (over and above the equipment required in standard care). The average number of units mean, on average how many pieces of equipment are required over a 72 hour period (e.g. 2 oxygen masks, 3 nasal tubes)? We do not need information on the amount of oxygen required per patient as we will be able to calculate this using trial data.

Equipment	Use of equipment for ROS in a stroke patient Average number of units per patient		Additional information to assist with costing e.g. manufacturer (if known)
	Treatment group 2 Night-time ROS for 72 hours	Treatment group 3 Continuous ROS for 72 hours	
Oxygen tubing(s)			
Portable oxygen cylinder			
Nasal tubes			
Oxygen mask (Venturi mask, MC mask)			

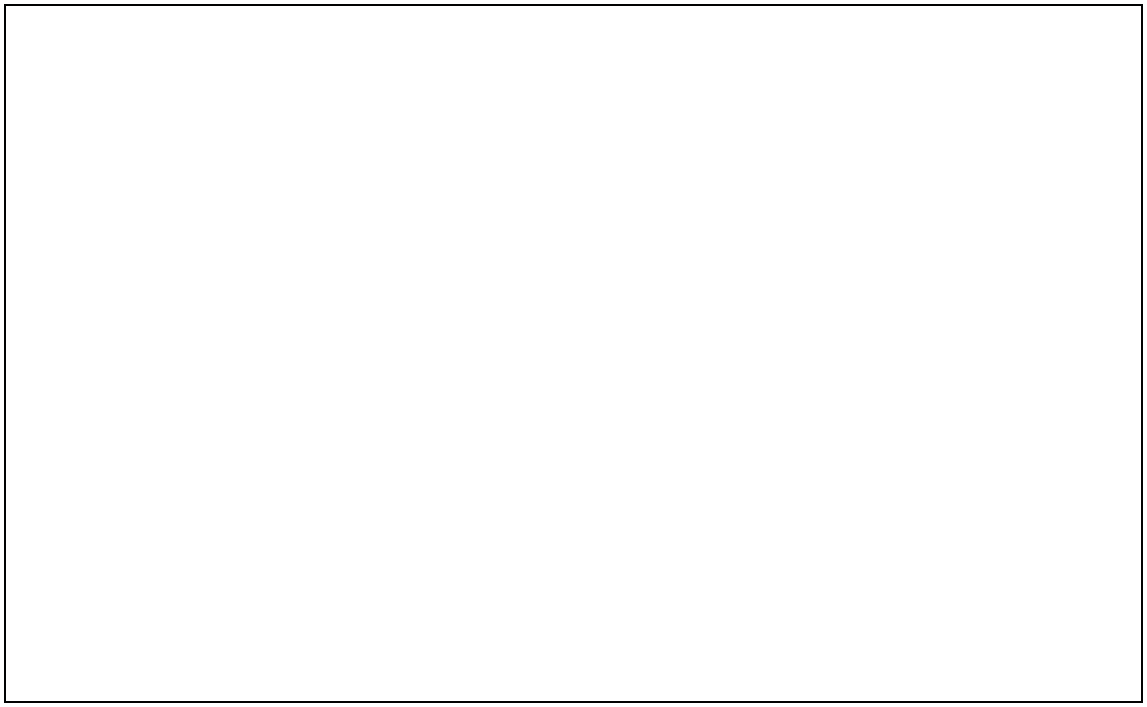
Other (please specify)*			

*Please, indicate if there is a piece of equipment normally used by your institution in ROS for stroke patients which is not included here

3. Please answer the following questions as accurate as possible:

Questions	Answers
What was the percentage of patients using masks?	
What was the percentage of patients in a cannula	
What was the percentage of patients having oxygen from a bottle	
Do you use dehumidifiers with the cannula?	
Do you use dehumidifiers with the oxygen mask?	
If a patient had a scan did they have the oxygen disconnected during the scan? Or did the patient have a scan with the oxygen bottle?	
How often things get replaced over 3 days?	
Other comments or further clarification?	

4. If you have any further information which you feel may be useful in our estimation of ROS costs, please write it here.



Thank you for your time

Appendix 4 Further details on multiple imputation of missing European Quality of Life-5 Dimensions, three levels data

We used methods suggested by Royston *et al.*[94] regarding the rule of thumb that the number of cycles for MI should be at least equal to the percentage of incomplete cases of the data set. In addition, when variables with missing values to be imputed are highly correlated (which was the case in our data) the index EQ-5D values at 3, 6 and 12 months were highly correlated (–0.7 and more), and more than 10 cycles of MI were needed for convergence. We used 25 cycles of imputation.

The predictive mean matching approach was used, because the predicted missing value from the imputation model is replaced with the closest (5) values from the observed complete EQ-5D-3L index. This method is used when you want to restrict the imputed values to be within the range observed for the imputed variable (–0.594 and 1 in the case of the EQ-5D index).

The following model was used:

mi impute chained (pmm, knn(5)) val_set_3m (pmm, knn(5)) value_set_6m (pmm, knn(5))
value_set_12m = age_atrand sex patienttreatment nih_score patient_risks

> core pat_randoxig sat, add(25)

Where pmm stands for prediction mean matching, knn refers to the number of closest values from where a missing figure would be imputed, and add(25) refers to the number of cycles of MI included.

EME
HS&DR
HTA
PGfAR
PHR

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