Stroke Oxygen Study Protocol and Statistical Analysis Plan:

1. Changes from the original to the final protocol

The first trial protocol was designed and approved before funding was obtained. Early changes reflect details of the NIHR RfPB grant. Further changes were related to change of funder to NIHR HTA. Please find a listing of changes below. Changed sections are highlighted in yellow in the final protocol for easier reference.

Title page (page 1):
Trial management group changed to trial management committee. Addition of trial manager and patient and public representatives.

Table of contents (page 2)
Updated to reflect additions to the protocol outlined below.

Trial summary (page 3)
Updated to include the results of the Stroke Oxygen Pilot Study.

Trial flow chart (page 4)
Updated to provide more detail, the SO_2Ss website, and contacts of the trial team.

General information and contacts (page 5)
Updated to reflect changes in committee membership between the start and the end of the trial, changes in contact details, and to include details of the sponsor, the funder and the research ethics committee.

Background (pages 6-7)
Updated to include additional references relating to reperfusion and hyperoxia, the results of the Stroke Oxygen Pilot Study, and national and international guidelines for the treatment of hypoxia.

Study protocol (pages 8-11)
Blinding: Details of blinding procedures added.
Initial assessment: More detailed instructions added.
Follow-up assessments: Follow-ups at 6 and 12 months added at the request of the funder (NIHR RfPB) to determine if any improvements gained early were maintained over time. More detailed information about processes relating to follow-up, blinding, and how to deal with non-responders.
Outcomes: the primary outcome (mRS) was moved from 6 months to 3 months to reflect changes in stroke outcome assessment over time (3-month mRS is now one of the most commonly used outcomes for stroke trials) (see page 12 of the final protocol for justification and references) and the primary outcome for the RfPB funded start-up phase of the trial. NIHSS change at one week was moved from a primary outcome to a secondary outcome, as it was considered that there should only be one primary outcome. To limit the number of secondary outcomes (18 in the original protocol)

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some of the outcomes (antibiotic use, sedative use, blood pressure, the outcomes generated by the patient focus group, as well as 6 and 12 month results) were re-defined as explanatory results.

Data management and evaluation (pages 12-13)
Statistical analysis: the original protocol contained a short and very general description of methods of analysis to be used. The final protocol contains a more detail of the statistical analysis, but remains very general. A detailed statistical analysis plan was developed after the final protocol was approved (Sim et al, 2014, attached below).
Study size: the original study size was estimated using parametric methods based on the mean mRS at 6 months in the first 200 patients in the SOS Pilot study. The study size calculation was updated using odds ratios to reflect non-parametric methods for analysis of the primary outcome for the main (NIHR HTA-funded) phase of the study, and confirmed the required study size of 6000. The study recruited extremely well. We were due to complete more than 1 year in advance of target. This gave us the opportunity to expand recruitment to 8000 within the budget provided by the NIHR HTA grant to allow us to increase the power for subgroup analyses, as an earlier study (Ronning and Guldvog, 1999) suggested that patients with severe strokes might be more likely to benefit.

Ethical requirements (page 13)
Updated to include the date of ethical approval and details of the ethics committee. Patient information sheets were updated and consent by an independent physician was added for patients who are incompetent to consent.

Monitoring of suspected unexpected serious adverse reactions (page 14)
This section was added to provide guidance monitoring of suspected unexpected serious adverse reactions.

Trial administration (pages 15 and 16)
This section was added to provide details of trial committees and their roles. The section on data monitoring and safety from the original protocol was included here.

Other
Correction of typos and section numbering as indicated.

1. Changes to the statistical analysis plan

There is only one statistical analysis plan for this study (Sim et al, 2014). This was followed in the analysis submitted here.

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