CONFIDENTIAL

Final Report for MHRA

Title: A cluster randomised trial of different strategies of antibiotic use to reduce the incidence and consequences of Post Stroke Pneumonia in acute stroke patients with swallowing problems: The STROKE-INF study.

EudraCT number: 2007-004298-24

Protocol: KCH-STR-INF v8.0, May 2014

Date of Report: 09/04/2015

Summary

Aim: To evaluate the effectiveness and safety of antibiotic prophylaxis for reducing PSP and improving mortality and functional outcomes in dysphagic stroke patients.

Methods: A multicentre prospective, cluster randomised, open-label trial with blinded end-point assessment was undertaken in 1217 dysphagic stroke patients recruited from 38 stroke units in the UK between 21/04/2009 and 17/05/2014. Patients clustered with centres were allocated to receive prophylactic antibiotics for 7 days in addition to standard care or only standard care within 48 hours of stroke onset. The primary outcome was PSP in the first 14 days, assessed using an objective, criteria-based, hierarchical algorithm and analysed using a generalized linear mixed model adjusted for patient and centre level covariates. Secondary outcomes included death, functional outcome at 90 days, duration of hospitalisation and antibiotic associated infections. Assessments and analyses were masked to allocation.

Results: Primary outcome was assessed in 602 control and 615 intervention patients; 18 (2.9%) control and 18 (2.9%) patients were lost to follow up at 90 days. Prophylactic antibiotics did not reduce the incidence of PSP (OR 1.32 [95% C.I. 0.73 - 2.40], p=0.358). There were no differences in all-cause mortality (OR 1.19 [95% C.I. 0.89-1.60], p=0.24) or functional outcomes at 90 days (OR 1.22 [95% CI 0.99-1.52], p=0.066). Antibiotic prophylaxis did not result in an increased occurrence of adverse events, including clostridium difficile diarrhoea and methicillin resistant staphylococcus aureus colonisation. Antibiotic prophylaxis increased the duration of hospitalisation (OR 1.14 [95%CI 1.02-1.24], p=0.02).

Interpretation: Antibiotic prophylaxis does not reduce PSP, mortality or functional disability but may increase hospitalisation in stroke patients with dysphagia managed on stroke units.

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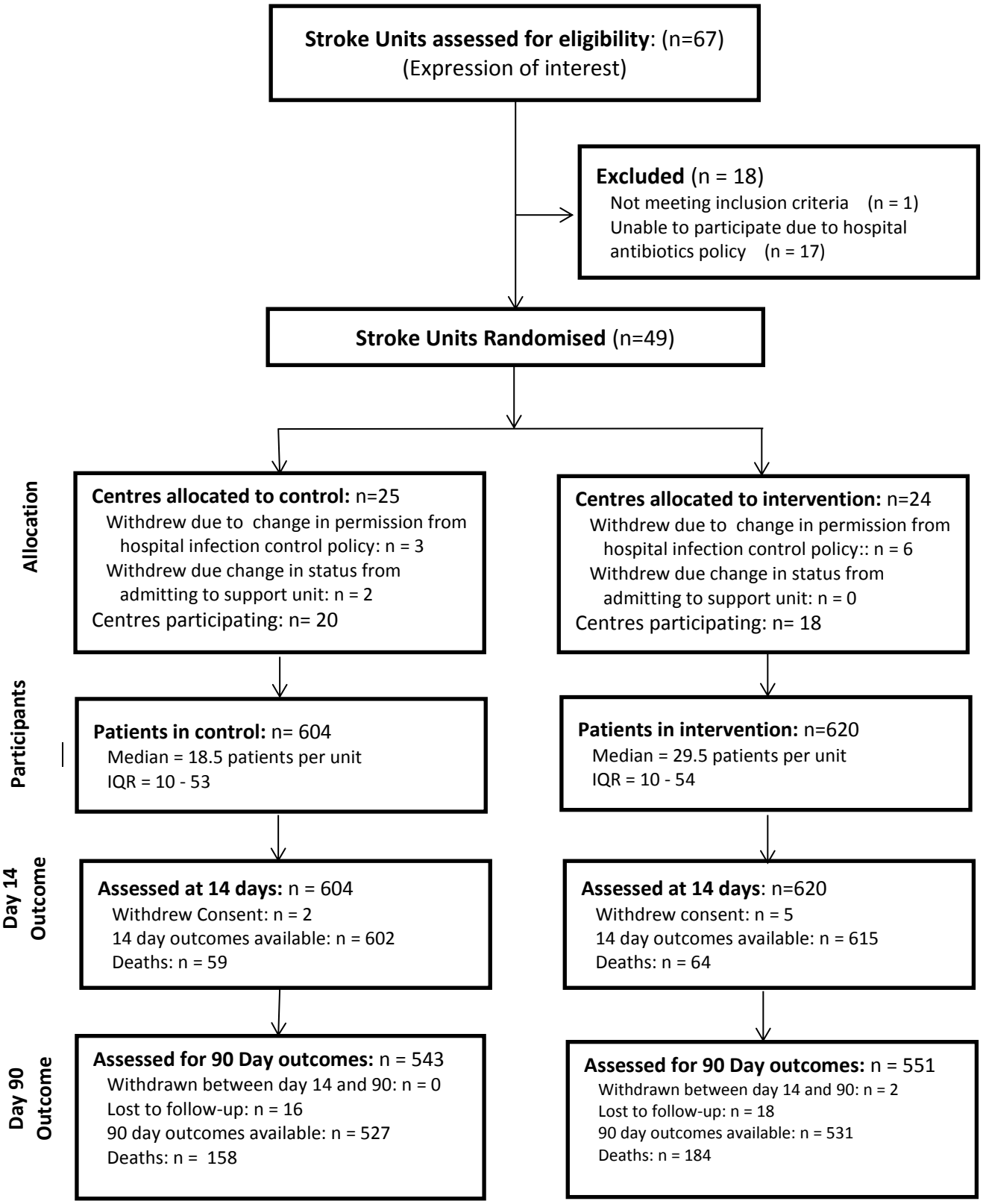
CONSORT Diagram



METHODS

Participants

Patients were eligible for participation if they were aged 18 years or older, had a confirmed primary diagnosis of new stroke (ischaemic or haemorrhagic; first or recurrent stroke), onset of symptoms ≤ 48 hours at recruitment and were unsafe to swallow on a bedside assessment performed by a trained assessor. Patients with pre-existing dysphagia, pyrexia, antibiotics in the week prior to admission or imminent death were excluded.

Randomisation

Centres were randomised on a 1:1 ratio to either the intervention or the control group using a minimisation algorithm. Randomisation was stratified for number of stroke admissions per year and the proportion of admitted directly to specialist care.

Sample size:

In a pooled analysis of 881 patients, the frequency of PSP was 22.3% (SD 7.9%) in dysphagic and 6.0% (SD 4.9%) in non-dysphagic patients.[1] In order to obtain 80% power to detect a difference between proportions of 22% and 10%, with an ICC of 0.05 for 25 clusters in each trial arm, 580 subjects were needed in each trial arm. A recruitment target 1200 subjects was set to allow for the actual attrition of 3%.

Intervention

All patients received guideline recommended care for dysphagia.Antibiotic choice conformed with local antibiotic policy at centres. If no restrictions were imposed, amoxicillin or co-amoxiclav alone or with clarithromycin were recommended. Antibiotics were initiated in dose, form and route recommended by local guidelines and given for 7 days.

Outcome Measures

Primary Outcome: PSP in the first 14 days, Diagnosis was based on the Centres for Disease Control and Prevention criteria for pneumonia, and confirmed using an objective hierarchical algorithm that interrogated 8 clinical/ laboratory observations at 6 time-points for:

1) Temperature ≥ 37.5°C on two consecutive measurements or a single measurement of ≥ 38.0°C **AND**
2) Respiratory rate ≥ 20 / min **OR** cough and breathlessness **OR** purulent sputum **AND**
3) White cell count >11.0 x 10^9/L **OR** chest infiltrates on X-ray **OR** positive sputum culture/microbiology **OR** positive blood culture.

The number of physician diagnosed PSP in the first 14 days was also recorded.

Secondary Outcomes: Death at 14 and 90 days, length of hospital stay and functional outcome at 90 days, defined by the modified Rankin Scale (mRS).

Safety Outcomes: *Clostridium difficile* infection was defined as diarrhoea in combination with a positive *C difficile* toxin test. Methicillin resistant staphylococcus aureus (MRSA) colonisation was defined as new positive isolates on between hospital admission and discharge.

Analysis:

Primary outcome: A generalized linear mixed model with PSP as outcome was used to take into account of patients being nested within centres. A fixed contrast for the treatment effect was included to determine the mean treatment effectiveness for intervention versus control group. Patient-level covariates in the model included age, sex, NIHSS score, pre-morbid mRS score, stroke type, previous strokes, thrombolysis, chronic lung disease and smoking. Centre level covariates were stroke admission per year and quartile ranking of the centre in the 2012 national stroke audit.

Secondary outcomes: Analysed using the same methodology as primary outcome. Rankin scale shift was assessed using ordinal regression. Group differences in length of hospital stay were assessed using cox regression. For the logistic and ordinal regressions a random intercept was included for each centre to to allow for differential statistical dependencies for patients within versus between centres.

Missing values: Generalized mixed models fitted under maximum likelihood automatically impute missing values using information from other cluster members. We strengthened missing at random (MAR) assumptions by including baseline predictors of missingness in the primary analysis model.

Subgroup analyses: These included assessing effectiveness of antibiotic prophylaxis in preventing PSP at 14 days according to age (<80 v ≥ 80 years), baseline stroke severity (NIHSS: 0-5, 6-15, 16-25, >25), thrombolysis, pre-morbid stroke mRS (0-2 v 3-5) and centre ranking (above or below national median).

Sensitivity analyses: Sensitivity analyses using more liberal thresholds for temperature, and also using physician-defined PSP, which takes into account subjective patient assessment. We analysed antibiotic use in both groups to assess "cross-over" of intervention and analysed outcomes in patients receiving 1, 3 or >3 days of antibiotics in both groups.

Analyses were performed using STATA software and two-tailed p values less than 0·05 were considered significant.

MAIN FINDINGS

Baseline Characteristics:

	Control N / Mean	% / SD	Intervention N / Mean	% / SD
N	602	49.5%	615	50.5%
Age at randomisation	78.4	10.9	77.7	11.9
(missing)	4 (0.6%)		0	
Male	265	43.1%	258	42.9%
(missing)	1 (0.2%)		3 (0.5%)	
Stroke Type				
Ischaemic	546	88.8%	545	90.5%
Haemorrhagic	69	11.2%	56	9.3%
(missing)	1 (0.1%)		0	
Thrombolysis	205	34.1%	192	31.2%
(missing)	3 (0.5%)		0	
NIHSS				
median (iqr)	14	9 - 20	15	9 -20
(missing)	3 (0.5%)		1 (0.2%)	
Pre-morbid mRS (0-2)	498	84%	490	80.9%
(missing)	9 (1.5%)		9 (1.5%)	
Antibiotics (0-7 days)				
Any antibiotics	207	34.4%	602	97.9%
(missing)	0		0	
Trial antibiotics(≥3 days)	1	0.2%	477	77.6%
Other antibiotics*	206	34.2%	125	20.3%

*Includes amoxicillin/coamoxaclav (in controls), cephalosporins (in controls), metronidazole, tazocin (pipercillin with tazobactam), gentamycin, flucloxacillin, trimtoprim, doxycycline, meropenem, ciprofloxacillin and vancomycin.

Primary and Secondary End points:

	Control	Intervention	OR (95% CI)	p	Adj OR (95% CI)	p
PSP at 14 days (Primary Outcome)						
Algorithm diagnosed	52/524 (9.9%)	71/564 (12.6%)	1.32 (0.73 – 2.44)	0.36	1.19 (0.67 – 2.15)*	0.54
Physician diagnosed**	99 / 602 (16.4%)	100 / 615 (16.3%)	1.00 (0.67 – 1.58)	0.89	0.98 (0.63 – 1.64)	0.95
Secondary Outcomes						
All-cause mortality at 90 days	158/586 (27%)	184/595 (30.9%)	1.21 (0.94-1.56)	0.13	1.19 (0.89-1.60)	0.24
mRS 0-2 at 90 days	121/586 (20.6%)	109/595 (18.3%)	0.86 (0.64-1.15)	0.31	0.86 (0.64-1.15)	0.31
Median stay in hospital (IQR)	19 (9 – 44)	26 (12 – 55.5)	1.13 (1.01 – 1.23)	0.03	1.14 (1.02 – 1.24)	0.02

* Sensitivity analyses under different assumptions (methods) did not show any differences between the control and the intervention groups.

**The agreement between algorithm and physician diagnosis of PSP was assessed and showed an actual agreement of 0.81 against an expected agreement 0.76 (k= 0.22).

PSP: Post stroke pneumonia; mRS: modified Rankin scale score (0-2) implies alive and independent; IQR: Intre-quartile range;

Serious Adverse Events by Treatment Group

Serious Adverse Events	Control	Intervention	OR (95%CI)	p
Infections				
All Infections (excluding PSP)	45/602 (7.5%)	22/615 (3.6%)	0.55 (0.32 - 0.92)	0.02
Diarrhoea (non-CDT)	5/602 (0.8%)	2/615 (0.3%)	0.39 (0.04 - 2.38)	0.28
Diarrhoea (CDT)	4/602 (0.7%)	2/615 (0.3%)	0.49 (0.04 - 3.33)	0.45
MRSA colonisation	14/602 (2.3%)	11/615 (1.8%)	0.76 (0.31 - 1.82)	0.55
Systemic				
CT confirmed stroke extension	22/602 (3.7%)	23/615 (3.7%)	1.03 (0.54 - 1.96)	0.98
Other Neurological including ICH	12/602 (2.0%)	14/615 (2.3%)	1.15 (0.49 - 2.78)	0.84
Gatrointestinal Bleed	6/602 (1.0%)	5/615 (0.8%)	0.81 (0.2 - 3.23)	0.77
Cardiac (MI, HF, Pul. oedema)	11/602 (1.8%)	15/615 (2.4%)	1.35 (0.57 - 3.23)	0.55
Elevated hepatic/renal enzymes	7/602 (1.1%)	8/615 (1.3%)	1.11 (0.35 - 3.7)	0.89
Transfer to intensive care	4/602 (0.7%)	6/615 (0.9%)	1.47 (0.35 - 7.14)	0.75
Miscellaneous	8/602 (1.4%)	6/615 (0.9%)	0.73 (0.21 - 2.33)	0.60

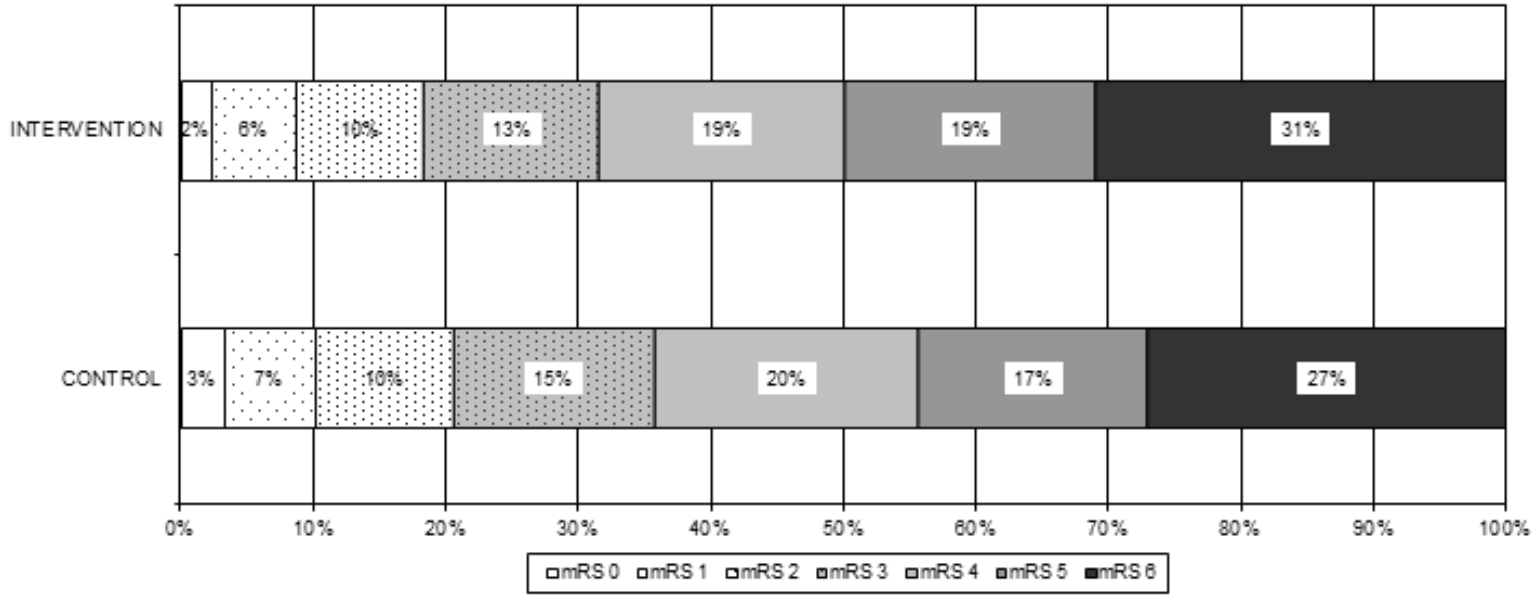
CDT: clostridium difficile toxin positive; MRSA: Methicillin resistant staphlococcus aureous; ICH: Intracranial haemorrhage; MI, HF, Pul. Oedema: Myocardial infarction, heart failure and pulmonary oedema.

There were 115 serious adverse events in the control group and 103 in the intervention group with no differences between the groups.

No allergic events were reported in either group.

group. ted in 13 (1%) patients and the incidence was comparable between the two groups

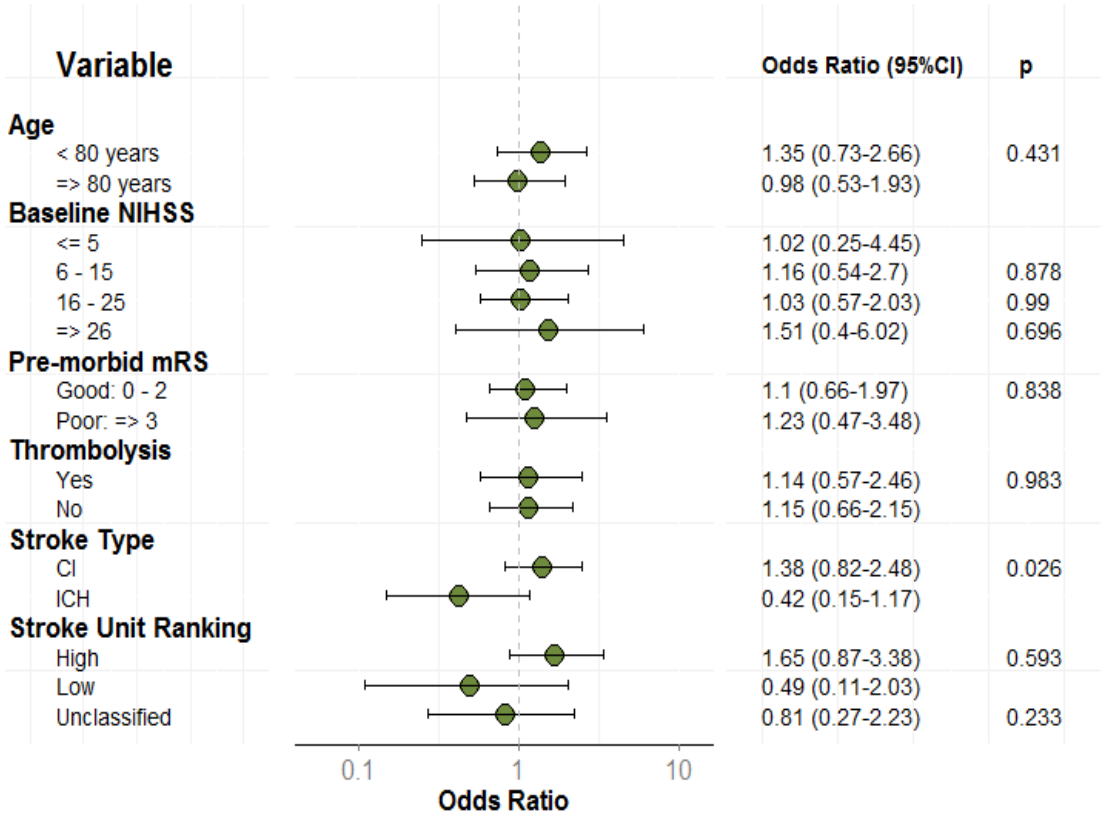
Distribution of modified Rankin Scale scores 3 months after randomisation



Unadjusted OR 1.22 (95% C.I. 0.99 -1.49), p=0.054
Adjusted OR 1.22 (95% C.I. 0.98-1.52), p=0.066

mRS = modified Rankin Scale. Scores on the scale range from 0 to 6, with 0 indicating no symptoms and 6 indicating death.

Pre-specified subgroup analysis for the Primary Outcome of PSP within 14 days



(OR <1.0 favours intervention; OR >1.0 favours control)

The primary outcome for the study was incidence of post-stroke pneumonia (PSP) within 14 days of randomisation.

NIHSS: National Institute of Health Stroke Scale score; mRS: Modified Rankin Scale
Stroke Unit Ranking: Above or below the national median in the 2012 National Stroke Audit. Unclassified are centres which did not submit data for the audit.

CONCLUSION

Antibiotic prophylaxis as a strategy did not reduce PSP or mortality, but was associated with longer hospitalisation and a possibility of higher dependency at 90 days.

STUDY GOVERNANCE

The trial protocol, statistical analysis plan, and detailed governance arrangements have been submitted as online supplementary material. The study (ISRCTN 37118456) was approved by the UK Medicines and Healthcare products Regulatory Agency (EudraCT No: 2007-004298-24), the West London National Research Ethics Committee (08/H0803/1) and the local Ethics Committee at each participating site.Oversight was provided by a Trials Steering Committee (TSC) and a Data Monitoring and Ethics Committee (DMEC) conforming to National Institute of Health Research guidelines.The trial was conducted in accordance with Good Clinical Practice (GCP). standard Data were monitored for quality and integrity by King's Healthcare Partners Clinical Trials Office (KHPCTO) using established verification and validation processes. Statistical analyses were performed in accordance with GCP and MHRA guidelines by the King's Clinical Trials Unit, Institute of Psychiatry, Psychology and Neurosciences, King's College London.

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Data Monitoring Committee *Professor Helen Rodgers (Chair), Dr Thomas Chadwick (Statistician), Mrs Sheila McCulloch (stroke patient and lay member); Dr Jonathan Edgeworth (Microbiology), Dr Paul Holmes (Neurology)*

Participating centres:

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