Clinical trial results:
A cluster randomised trial of different strategies of antibiotic use to reduce the incidence and consequences of chest infection in acute stroke patients with swallowing problems.

Summary

EudraCT number	2007-004298-24
Trial protocol	GB
Global end of trial date	18 September 2014

Results information

Result version number	v1 (current)
This version publication date	06 December 2018
First version publication date	06 December 2018
Summary attachment (see zip file)	FINAL STUDY REPORT (Final Report.pdf)

Trial information

Trial identification

Sponsor protocol code	KCH-STR-INF

Additional study identifiers

ISRCTN number	ISRCTN37118456
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	King's College Hospital
Sponsor organisation address	Denmark Hill, London, United Kingdom, SE59RS
Public contact	Professor Lalit Kalra, King's College Hospital NHS Foundation Trust, 0044 0203299 1718, lalit.kalra@kcl.ac.uk
Scientific contact	Professor Lalit Kalra, King's College Hospital NHS Foundation Trust, 0044 0203299 1718, lalit.kalra@kcl.ac.uk
Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Professor Lalit Kalra, King's College London, 0044 0203299 1718, lalit.kalra@kcl.ac.uk
Scientific contact	Professor Lalit Kalra, King's College London, 0044 0203299 1718, lalit.kalra@kcl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 September 2014
Global end of trial reached?	Yes
Global end of trial date	18 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main hypothesis for the study is that prophylactic use of antibiotics (an "act first" approach) in acute stroke patients with swallowing problems on a bedside clinical assessment will be better than the current practice of monitoring for infection and treatment if necessary (a "wait and watch" approach) in reducing chest infections and their consequences in stroke patients

Protection of trial subjects:

The study will be undertaken in hospital based stroke units that have a defined policy for acute stroke care and participate in the National Stroke Audit (NSA).

Background therapy:

not applicable

Evidence for comparator:

A Pragmatic cluster randomised controlled trial in 50 participating stroke units. Cluster randomisation at the stroke unit level for treatment or no treatment.

Actual start date of recruitment	01 January 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1224
Worldwide total number of subjects	1224
EEA total number of subjects	1224

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	160
From 65 to 84 years	678
85 years and over	386

Subject disposition

Recruitment

Recruitment details:

Between April 21, 2008, and May 17, 2014, we randomly assigned 48 stroke units (and 1224 patients clustered within the units) to the two treatment groups: 24 to antibiotics and 24 to standard care alone (control).

Pre-assignment

Screening details:

The inclusion criteria:
1. Ischaemic or hemorrhagic stroke confirmed on CT imaging
2. Recruited within 48 hours of symptom onset
3. Unable to tolerate normal diet or fluids because of
a. impaired consciousness levels.
b. failed clinical bedside swallowing assessment performed by a trained assessor
c. "nil orally" orders, nasogastric tubes, mo

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Cluster-randomised, open-label controlled trial. 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

Arms

Are arms mutually exclusive?	Yes
Arm title	Antibiotic Intervention

Arm description:

Patients received prophylactic antibiotics for 7 days plus standard stroke unit care

Arm type	Experimental
Investigational medicinal product name	Amoxicillin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion, Powder and solvent for oral solution
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Administered according to local practice for 7 days

Investigational medicinal product name	Clarithromycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion, Powder for oral solution, Powder for oral solution in sachet, Powder for oral suspension
Routes of administration	Intravenous drip use , Oral use

Dosage and administration details:

Administered according to local policy and care for 7 days

Investigational medicinal product name	Metronidazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution, Powder and solvent for solution for injection/infusion, Oral emulsion

Routes of administration	Oral use, Intravenous drip use
Dosage and administration details: Administered according to local practice and care for 7 days	
Investigational medicinal product name	Trimethoprim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid, Oral solution, Oral suspension, Powder and solvent for solution for infusion
Routes of administration	Intravenous use, Oral use
Dosage and administration details: Administered according to local practice and care for 7 days	
Arm title	Control Arm
Arm description: Standard clinical care with no intervention.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Antibiotic Intervention	Control Arm
Started	620	604
Completed	413	428
Not completed	207	176
Consent withdrawn by subject	5	2
Death due to disease (secondary endpoint)	184	-
Lost to follow-up	18	16
Death due to disease (secondary endpoi	-	158

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	1224	1224	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	160	160	
From 65-84 years	678	678	
85 years and over	386	386	
Gender categorical Units: Subjects			
Female	696	696	
Male	528	528	

End points

End points reporting groups

Reporting group title	Antibiotic Intervention
Reporting group description:	
Patients received prophylactic antibiotics for 7 days plus standard stroke unit care	
Reporting group title	Control Arm
Reporting group description:	
Standard clinical care with no intervention.	

Primary: Clinical Endpoint

End point title	Clinical Endpoint[1]
End point description:	
The clinical primary outcome measure is the incidence of PSP in the first 14 days after stroke onset or prior to discharge home if sooner. This will be defined as temperature >37.5°C on two consecutive measurements or a single measurement of >38.0°C with chest symptoms and one or more of the following: white cell count >11 000/mL, pulmonary infiltrate on chest x-rays, positive microbiology cultures.[2,8-10] The diagnosis of PSP will be adjudicated independently by non-participating clinicians masked to treatment allocation based on anonymised clinical information submitted by centres.	
End point type	Primary
End point timeframe:	
0 to 90 days post Stroke	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Please see attached document for results.	

End point values	Antibiotic Intervention	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	428		
Units: whole	413	428		

Attachments (see zip file)	Results/Stroke INF In J Stroke 2018.pdf SAE LINE LISTING/Stroke INF SAE line listing 2015.pdf

Statistical analyses

No statistical analyses for this end point

Primary: Primary Economic Endpoint

End point title	Primary Economic Endpoint[2]
End point description:	
The primary cost outcome measure will be the total hospital costs (acute and rehabilitation) for the initial episode of care, calculated as a product of costs per unit of each type of care (standardised NHS tariff) and amount used, using methodology validated previously	
End point type	Primary

End point timeframe:

Duration of the trial

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Please see attached document for results.

End point values	Antibiotic Intervention	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	428		
Units: whole	413	428		

Attachments (see zip file)	Results Lancet/Stroke INF Lancet.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Death

End point title	Death

End point description:

At 14 days:
1. Death, death or PSP at 14 days of stroke onset
2. National Institute of Health Stroke Scale (NIHSS) at 14 days of stroke onset or at discharge if sooner
3. Change in NIHSS from baseline at 14 days of stroke onset or at discharge if sooner
4. Discontinuation of antibiotic prophylaxis in the intervention group (< 4 days of treatment)
5. Antibiotic use in the control group within 7 days of stroke onset
6. Duration of hospital stay if ≤14 days
7. Participation in programmed assessment or therapy activities, measured as the number and duration of supervised rehabilitation during hospital stay.
8. C. difficile diarrhoea
9. New onset of MRSA infection
10. Per protocol Adverse Event (AE), Adverse Reaction (AR), Serious Adverse Event / Reaction (SAE / SAR), and Suspected Unexpected Serious Adverse Reactions (SUSAR).

End point type	Secondary

End point timeframe:

0 to 14 days

End point values	Antibiotic Intervention	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	428		
Units: whole	413	428		

Statistical analyses

No statistical analyses for this end point

Secondary: Death & Clinical/ Economic endpoints

End point title	Death & Clinical/ Economic endpoints

End point description:

At 90 days:
11. Modified Rankin Scale at 90 (± 14) days post-stroke
12. Patients achieving dichotomised modified Rankin Scale score (mRS 0-2) at 90 (± 14) days post-stroke
13. Ordinal regression analysis of mRS at 90 (± 14) days post stroke
14. Mortality, institutionalisation and mortality or institutionalisation at 90 (± 14) days post stroke
15. Duration of hospital stay if >14 days
16. Incident chest infections between 15-90 days
17. Barthel Index at 90 (± 14) days
18. EUROQOL scores at 90 (± 14) days post stroke.
19. Incremental cost-effectiveness ratios (ICERs) if either the intervention or control approach involves an additional cost alongside an improvement in outcome (ICERs will then represent the cost per 1% reduction in incidence of PSP and/or cost per quality-adjusted life-year (QALY) gained).

End point type	Secondary

End point timeframe:

At 90 days post Stroke

End point values	Antibiotic Intervention	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	428		
Units: whole	413	428		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Until 90 day timepoint

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Antibiotic Intervention

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Please see attached document for adverse event descriptions.

Serious adverse events	Antibiotic Intervention		
Total subjects affected by serious adverse events			
subjects affected / exposed	109 / 620 (17.58%)		
number of deaths (all causes)	184		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Cardiac (MI, HF, Pul. oedema)			
subjects affected / exposed	15 / 620 (2.42%)		
occurrences causally related to treatment / all	0 / 15		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
CT confirmed stroke extension			
subjects affected / exposed	23 / 620 (3.71%)		
occurrences causally related to treatment / all	0 / 23		
deaths causally related to treatment / all	0 / 0		
Other Neurological including ICH			
subjects affected / exposed	14 / 620 (2.26%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Transfer to intensive care			

subjects affected / exposed	6 / 620 (0.97%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Miscellaneous				
subjects affected / exposed	6 / 620 (0.97%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Gatrointestinal Bleed				
subjects affected / exposed	5 / 620 (0.81%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Elevated hepatic/renal enzymes				
subjects affected / exposed	8 / 620 (1.29%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
All Infections (excluding PSP)				
subjects affected / exposed	22 / 620 (3.55%)			
occurrences causally related to treatment / all	0 / 22			
deaths causally related to treatment / all	0 / 0			
Diarrhoea (non-CDT)				
subjects affected / exposed	2 / 620 (0.32%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea (CDT)				
subjects affected / exposed	2 / 620 (0.32%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
MRSA colonisation				
subjects affected / exposed	11 / 620 (1.77%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 0			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Antibiotic Intervention		
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 620 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 September 2008	Addition of co-sponsor.
04 June 2009	Addition to Participant Exclusion Criteria:- Expected survival <2 weeks under exclusion criteria
19 October 2009	Change to IMP storage conditions 1. Old Text – Page 9 "IMPs must be stored in a temperature controlled environment (oC) with restricted access to unauthorized personnel." 2. New Text – page 8, exclusion criteria "IMPs must be stored in a temperature controlled environment (stored according to manufactures instructions) with restricted access to unauthorized personnel." Change of PI at one site.
25 January 2010	Protocol changes to consent and recruitment procedures:- 1. Old Text – Page 8, Recruitment and Consent Procedures "If a patient is unable to give written consent because of stroke related deficits such as arm weakness or dysphasia, assent for inclusion will be obtained from the next of kin or relatives. Written consent to support the assent will be sought as soon as the patient is able to provide this consent." 2. New Text – page 8, Recruitment and Consent Procedures "In circumstances where the patient can read and understand the information on the patient information sheet but is unable to sign due to stroke related deficits such as arm weakness, a researcher or a witness can attest that any mark they make is their signature to consent. Additionally if the patient is able to understand but is unable make a mark due to stroke deficits, an independent witness can countersign the consent form for patient. This witness can be the researcher. Addition of 8 new clinical sites and change of PI at one existing site.
16 September 2011	1. The duration of the study has been extended up to June 2013 reflecting the current recruitment rates for the study. 2. References to specific recommended antibiotics have been removed from objectives (1) and replaced with prophylactic antibiotics. 3. Objective (3) stated that we will be measuring functional independence, this is not the case, and therefore the statement has been updated. 4. The original recruitment rates in individual centres of 5.6 patients/centre/ month have not been met because of changes in organistaion of stroke services and limited recruitment over weekends. This has changed to a new recruitment target of 2 patients/ centre/ month over a 24 month period. 5. The 4th exclusion criteria have been updated to include "other antibiotics". 6. Both the health intervention and IMP section in the protocol have been simplified stating that prophylactic treatment will be initiated in dose, form and route in accordance with local hospital antibiotics and infection control policies. It now also includes the addition of the two IMPs (metronidazole and co-trimoxazole) which have been added as they are the preferred antibiotic regime to be used by Charing Cross Hospital (Imperial College Healthcare NHS Trust). 7. References to chest x-ray have been replaced with a statement to the effect that the treatment for patients with raised temperature will follow normal clinical management, and results will be recorded in the CRF.

17 September 2014	Chest infections have been replaced by Post Stroke Pneumonia (PSP) throughout the protocol The sample size has been updated to reflect a reduced attrition rate. The primary endpoint has been changed from chest infection to post stroke pneumonia based on TSC adjudication. Statistical analysis section of the protocol now provides details of analytical methods. The following non-substantial changes have also been incorporated into this amendment and these have been included in the submission: Page 1: Short title added Change in CI details Change in trial duration Page 4: The trial flow has been refined to be clearer, no change in design Page 5: 2nd paragraph (background) updated Page 7: Inclusion criteria unchanged but presented more clearly Page 10: Secondary endpoints reformatted for better visualisation, otherwise unchanged. Page 15The names of the Chair and members of the TMG, TSC and DMEC have been added. Page 16 Publication Policy added

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Selection bias, especially in a cluster-randomised trial, could result from patients at increased risk of post-stroke pneumonia being recruited preferentially to the antibiotic intervention group. But no differences noted in baseline characteristics.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30196790

http://www.ncbi.nlm.nih.gov/pubmed/26343840