Clinical trial results:
Minimally Invasive Surgery plus rt-PA for ICH Evacuation

Summary

EudraCT number	2007-006006-22
Trial protocol	GB DE
Global end of trial date	08 April 2013

Results information

Result version number	v1 (current)
This version publication date	17 October 2019
First version publication date	17 October 2019

Trial information

Trial identification

Sponsor protocol code	ICH01

Additional study identifiers

ISRCTN number	ISRCTN00224770
ClinicalTrials.gov id (NCT number)	NCT00224770
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Johns Hopkins University
Sponsor organisation address	750 East Pratt Street, 16th Floor, Baltimore, United States, 21202
Public contact	Daniel Hanley, MD, Johns Hopkins University, +1 410-361-7999, dhanley@jhmi.edu
Scientific contact	Daniel Hanley, MD, Johns Hopkins University, +1 410-361-7999, dhanley@jhmi.edu
Sponsor organisation name	Newcastle upon Tyne Hospitals NHS Trust
Sponsor organisation address	Joint Research Office, R&D Dept, 4th Floor, Leazes Wing, Royal Victoria Infirmary, Queen Victoria Ro, Newcastle upon Tyne, United Kingdom, NE1 4LP
Public contact	Amanda Tortice, Newcastle upon Tyne Hospitals NHS Trust , 0191 282 5959, amanda.tortice@nuth.nhs.uk
Scientific contact	Amanda Tortice, Newcastle upon Tyne Hospitals NHS Trust , 0191 282 5959, amanda.tortice@nuth.nhs.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	02 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 April 2013
Global end of trial reached?	Yes
Global end of trial date	08 April 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the safety of minimally invasive surgery plus aspiration followed by the administration of a low dose of recombinant tissue plasminogen activator (rt-PA; Activase, Genentech, Inc., San Francisco, CA) to intracerebral hemorrhage patients (ICH) via a catheter inserted directly into the clot and to assess its ability to remove blood clot from the brain tissue

Protection of trial subjects:

The risks of initial haematoma growth/instability were managed by use of a stability protocol combining normalization of coagulation parameters, BP management, and repeat computed tomography (CT) assessment of clot size, measured using the ABC/2 method. Six or more hours after the diagnostic CT, a stability CT was performed to ensure that the ICH clot had not expanded by >5 mL, providing image demonstration of a safe starting point for clot reduction therapy, defined as the absence of active bleeding before performing MIS+rt-PA. The CT could be repeated every six hours until the clot stabilized or just before the 48-hour eligibility window closed, whichever came first. In addition, a magnetic resonance image (MRI) or CT angiography (CTA) was required to rule out underlying pathology as the bleeding source; an angiogram was encouraged with equivocal findings on vascular pathology screening. An INR ≤1.3, a normal aPTT, and BP stability were required prior to randomization. After a protocol amendment, planned catheter insertion trajectories describing the skull entry site and the planned linear path to the hematoma target were shared by the site with the trial's Surgical Center for joint review (stage two only).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 108
Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	110
EEA total number of subjects	2

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)	52
From 65 to 84 years	58
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

110 patients were randomized to the trial, and 31 were recruited as pilot patients.
The decision was made to exclude the pilot patients from the analysis

Pre-assignment

Screening details:

Each study center was required to demonstrate proficiency in the technical aspects of enrollment, stabilization, surgery, and drug administration. This proficiency was demonstrated on at least one pilot patient prior to randomization of the first patient in the investigational cohort of 110 randomized patients

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Medical Management

Arm description:

Standard of care medical management as per American Heart Association (AHA) guidelines.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	MISTIE Surgical Management

Arm description:

Minimally invasive surgery (MIS) with clot lysis with recombinant tissue plasminogen activator (rt-PA)

Arm type	Active comparator
Investigational medicinal product name	Cathflo Activase
Investigational medicinal product code	
Other name	rtPA, Alteplase
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intracerebral use

Dosage and administration details:

Minimally invasive surgery (MIS) with clot lysis with recombinant tissue plasminogen activator (rt-PA). MIS+Cathflo Activase (drug): The intervention is a comparison of the safety and preliminary effectiveness of
investigational minimally invasive surgery to place a catheter into an intracerebral hemorrhage blood clot and
subsequent administration in sequential tiers of 0.3 or 1.0mg of rt-PA, CathFlo® through the catheter once
every eight hours for up to 72 hours, in addition to best medical care. This includes 54 intent-to-treat patients, and excludes 27 pilots.

Arm title	ICES Surgical Management

Arm description:

Intraoperative stereotactic CT-Guided Endoscopic Surgery

Arm type	Intraoperative stereotactic CT-Guided Endoscopic S

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Medical Management	MISTIE Surgical Management	ICES Surgical Management
Started	42	54	14
Completed	38	52	14
Not completed	4	2	0
Lost to follow-up	4	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Medical Management
Reporting group description:	
Standard of care medical management as per American Heart Association (AHA) guidelines.	
Reporting group title	MISTIE Surgical Management
Reporting group description:	
Minimally invasive surgery (MIS) with clot lysis with recombinant tissue plasminogen activator (rt-PA)	
Reporting group title	ICES Surgical Management
Reporting group description:	
Intraoperative stereotactic CT-Guided Endoscopic Surgery	

Reporting group values	Medical Management	MISTIE Surgical Management	ICES Surgical Management
Number of subjects	42	54	14
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	18	25	9
From 65-84 years	24	29	5
85 years and over	0	0	0
Age continuous Units: years			
median	62	60	59
inter-quartile range (Q1-Q3)	49.5 to 73	54 to 69	53.2 to 68.2
Gender categorical Units: Subjects			
Female	14	19	5
Male	28	35	9
Region of Enrollment			
Number of enrollments by region			
Units: Subjects			
United Kingdom	41	53	0
United States	1	1	14

Reporting group values	Total		
Number of subjects	110		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	52		
From 65-84 years	58		
85 years and over	0		
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical			
Units: Subjects			
Female	38		
Male	72		
Region of Enrollment			
Number of enrollments by region			
Units: Subjects			
United Kingdom	94		
United States	16		

End points

End points reporting groups

Reporting group title	Medical Management
Reporting group description:	
Standard of care medical management as per American Heart Association (AHA) guidelines.	
Reporting group title	MISTIE Surgical Management
Reporting group description:	
Minimally invasive surgery (MIS) with clot lysis with recombinant tissue plasminogen activator (rt-PA)	
Reporting group title	ICES Surgical Management
Reporting group description:	
Intraoperative stereotactic CT-Guided Endoscopic Surgery	

Primary: Rate of Mortality

End point title	Rate of Mortality
End point description:	
Percentage of participants who died during the first 30 days after randomization.	
End point type	Primary
End point timeframe:	
30 days from randomization	

End point values	Medical Management	MISTIE Surgical Management	ICES Surgical Management	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	54	14	
Units: Percentage of participants				
number (confidence interval 90%)	9.5 (3.3 to 20.5)	14.8 (7.6 to 25.1)	7.1 (0.4 to 29.7)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Null hypothesis is that rate of mortality within 30 days is the same between the two groups. The alternative hypothesis tests whether MISTIE surgical management has a higher rate of mortality than the medical arm.	
Comparison groups	Medical Management v MISTIE Surgical Management
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.324
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	5.3

Confidence interval	
level	95 %
sides	1-sided
upper limit	16.2
Variability estimate	Standard error of the mean
Dispersion value	6.6

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Null hypothesis is that rate of mortality within 30 days is the same between the two groups. The alternative hypothesis tests whether ICES surgical management has a higher rate of mortality than the medical arm.

Comparison groups	Medical Management v ICES Surgical Management
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.633
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-2.4
Confidence interval	
level	95 %
sides	1-sided
upper limit	11.2
Variability estimate	Standard error of the mean
Dispersion value	8.2

Primary: Rate of Procedure-related Mortality

End point title	Rate of Procedure-related Mortality

End point description:

Percentage of participants who died during the first 7 days after randomization.

End point type	Primary

End point timeframe:

7 days from randomization

End point values	Medical Management	MISTIE Surgical Management	ICES Surgical Management	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	54	14	
Units: Percentage of particpants				
number (confidence interval 90%)	0 (0 to 6.9)	5.6 (1.5 to 13.7)	0 (0 to 19.3)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Medical Management v MISTIE Surgical Management
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.174
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	5.6
Confidence interval	
level	95 %
sides	1-sided
upper limit	11.7
Variability estimate	Standard error of the mean
Dispersion value	3.1

Primary: Rate of Cerebritis, Meningitis, Bacterial Ventriculitis	
End point title	Rate of Cerebritis, Meningitis, Bacterial Ventriculitis
End point description: Percentage of participants who had a bacterial brain infection (cerebritis, meningitis, ventriculitis) within 30 days of randomization.	
End point type	Primary
End point timeframe: 30 days from randomization	

End point values	Medical Management	MISTIE Surgical Management	ICES Surgical Management	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	54	14	
Units: Percentage of participants				
number (confidence interval 90%)	2.4 (0.1 to 10.8)	0 (0 to 5.4)	0 (0 to 19.3)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Null hypothesis is that rate of cerebritis, meningitis and ventriculitis within 30 days is the same between the two groups. The alternative hypothesis tests whether MISTIE surgical management has a higher rate of these infections than medical.	
Comparison groups	Medical Management v MISTIE Surgical Management
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.437
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-2.4
Confidence interval	
level	95 %
sides	1-sided
upper limit	1.5
Variability estimate	Standard error of the mean
Dispersion value	2.4

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Null hypothesis is that rate of cerebritis, meningitis and ventriculitis within 30 days is the same between the two groups. The alternative hypothesis tests whether ICES surgical management has a higher rate of these infections than medical.	
Comparison groups	Medical Management v ICES Surgical Management
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.75
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-2.4
Confidence interval	
level	95 %
sides	1-sided
upper limit	1.5
Variability estimate	Standard error of the mean
Dispersion value	2.4

Primary: Rate of symptomatic rebleeding	
End point title	Rate of symptomatic rebleeding
End point description:	
The difference in the rate of symptomatic rebleeding 72 hours post last dose.	
End point type	Primary
End point timeframe:	
72 hours post last dose	

End point values	Medical Management	MISTIE Surgical Management	ICES Surgical Management	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	54	14	
Units: Percentage of participants				
number (confidence interval 90%)	2.4 (0.1 to 10.8)	5.6 (1.5 to 13.7)	0 (0 to 19.3)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Null hypothesis is that rate of symptomatic rebleeding 72 hours post last dose is the same between the two groups. The alternative hypothesis tests whether MISTIE surgical management has a higher rate of symptomatic rebleeding than the medical arm.

Comparison groups	Medical Management v MISTIE Surgical Management
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.409
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	3.2
Confidence interval	
level	95 %
sides	1-sided
upper limit	9.6
Variability estimate	Standard error of the mean
Dispersion value	3.9

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Null hypothesis is that rate of symptomatic rebleeding 72 hours post last dose is the same between the two groups. The alternative hypothesis tests whether ICES surgical management has a higher rate of symptomatic rebleeding than the medical arm.

Comparison groups	Medical Management v ICES Surgical Management
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.75
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-2.4

Confidence interval	
level	95 %
sides	1-sided
upper limit	2.2
Variability estimate	Standard error of the mean
Dispersion value	2.4

Primary: Dichotomized Modified Rankin Scale (mRS) at day 180

End point title	Dichotomized Modified Rankin Scale (mRS) at day 180

End point description:

Percentage of participants with dichotomized mRS score in 0-3 range. The mRS measures the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. The scale ranges from 0-6: (0) no symptoms at all, (1) no significant disability despite symptoms; able to carry out all usual duties and activities, (2) slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance, (3) moderate disability; requiring some help, but able to walk without assistance, (4) moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance, (5) severe disability; bedridden, incontinent and requiring constant nursing care and attention, (6) dead

End point type	Primary

End point timeframe:

180 days from randomization

End point values	Medical Management	MISTIE Surgical Management	ICES Surgical Management	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38[1]	52[2]	14	
Units: Percentage of participants				
number (confidence interval 90%)	23.7 (12.9 to 37.7)	34.6 (23.7 to 46.9)	42.9 (20.6 to 67.5)	

Notes:

[1] - All patients with non-missing mRS score at 180 days were analysed

[2] - All patients with non-missing mRS score at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Null hypothesis is that the proportion with mRS score of 0-3 at 180 days is the same between the two groups. The alternative hypothesis tests whether MISTIE surgical management has a higher proportion than the medical arm.

Comparison groups	Medical Management v MISTIE Surgical Management
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.189
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	10.9

Confidence interval	
level	95 %
sides	1-sided
upper limit	26.6
Variability estimate	Standard error of the mean
Dispersion value	9.5

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Null hypothesis is that the proportion with mRS score of 0-3 at 180 days is the same between the two groups. The alternative hypothesis tests whether ICES surgical management has a higher proportion than the medical arm.

Comparison groups	Medical Management v ICES Surgical Management
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.156
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	19.2
Confidence interval	
level	95 %
sides	1-sided
upper limit	43.7
Variability estimate	Standard error of the mean
Dispersion value	14.9

Secondary: Ordinal Modified Rankin Scale (mRS) at Day 180

End point title	Ordinal Modified Rankin Scale (mRS) at Day 180

End point description:

Ordinal distribution of the Modified Rankin Scale score at 180 days. The mRS measures the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. The scale ranges from 0-6: (0) no symptoms at all, (1) no significant disability despite symptoms; able to carry out all usual duties and activities, (2) slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance, (3) moderate disability; requiring some help, but able to walk without assistance, (4) moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance, (5) severe disability; bedridden, incontinent and requiring constant nursing care and attention, (6) dead.

End point type	Secondary

End point timeframe:

180 days from randomization

End point values	Medical Management	MISTIE Surgical Management	ICES Surgical Management	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38[3]	52[4]	14	
Units: Unit on a scale				
median (inter-quartile range (Q1-Q3))	4 (4 to 6)	4 (3 to 6)	4 (3 to 5)	

Notes:

[3] - All patients with non-missing mRS scores at 180 days were analysed

[4] - All patients with non-missing mRS scores at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Null hypothesis is that the distributions of the mRS values for both groups are the same. The alternative hypothesis is that the distributions are not the same.

Comparison groups	MISTIE Surgical Management v Medical Management
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.468
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

are the same. The alternative hypothesis is that the distributions are not the same.

Comparison groups	Medical Management v ICES Surgical Management
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.294
Method	Wilcoxon (Mann-Whitney)

Secondary: Ordinal Modified Rankin Scale (mRS) at Day 365

End point title	Ordinal Modified Rankin Scale (mRS) at Day 365

End point description:

Ordinal distribution of the Modified Rankin Scale score at 365 days. The mRS measures the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. The scale ranges from 0-6: (0) no symptoms at all, (1) no significant disability despite symptoms; able to carry out all usual duties and activities, (2) slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance, (3) moderate disability; requiring some help, but able to walk without assistance, (4) moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance, (5) severe disability; bedridden, incontinent and requiring constant nursing care and attention, (6) dead.

End point type	Secondary

End point timeframe:

365 days from randomization

End point values	Medical Management	MISTIE Surgical Management	ICES Surgical Management	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24[5]	20[6]	12[7]	
Units: Units on a scale				
median (inter-quartile range (Q1-Q3))	4.5 (3.5 to 6)	4 (2 to 6)	3.5 (3 to 5)	

Notes:

[5] - All patients with non-missing mRS score at day 365 were analysed

[6] - All patients with non-missing mRS score at day 365 were analysed

[7] - All patients with non-missing mRS score at day 365 were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Null hypothesis is that the distributions of the mRS values for both groups are the same. The alternative hypothesis is that the distributions are not the same.

Comparison groups	Medical Management v MISTIE Surgical Management
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.395 [8]
Method	Wilcoxon (Mann-Whitney)

Notes:

[8] - Two-sided test

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Null hypothesis is that the distributions of the mRS values for both groups are the same. The alternative hypothesis is that the distributions are not the same.

Comparison groups	Medical Management v ICES Surgical Management
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.175 [9]
Method	Wilcoxon (Mann-Whitney)

Notes:

[9] - Two-sided test

Secondary: Clot size reduction by end of treatment

End point title	Clot size reduction by end of treatment

End point description:

The percentage of blood clot resolved by the end of treatment CT scan compared to the stability CT scan.

End point type	Secondary

End point timeframe:

Time from randomization until end of treatment, up to 10 days

End point values	Medical Management	MISTIE Surgical Management	ICES Surgical Management	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	54	14	
Units: percentage of blood clot resolved				
median (inter-quartile range (Q1-Q3))	3.9 (-0.06 to 10.2)	64.3 (43.3 to 74.1)	69.5 (59.0 to 86.0)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Null hypothesis is that the distributions of percentage of blood clot resolved are the same between the two groups. The alternative hypothesis is that the distributions are not the same.

Comparison groups	Medical Management v MISTIE Surgical Management
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Wilcoxon (Mann-Whitney)

Notes:

[10] - Two-sided test

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Null hypothesis is that the distributions of percentage of blood clot resolved are the same between the two groups. The alternative hypothesis is that the distributions are not the same.

Comparison groups	Medical Management v ICES Surgical Management
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Wilcoxon (Mann-Whitney)

Notes:

[11] - Two-sided test

Secondary: Post-operative clot size reduction among surgical patients

End point title	Post-operative clot size reduction among surgical patients[12]

End point description:

The percentage of blood clot resolved by the end of treatment CT scan compared to the post-operative CT scan for MISTIE surgical patients.

End point type	Secondary

End point timeframe:

Time from post-operation until end of treatment, up to 10 days

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point description says "Post-operative clot size reduction among surgical patients", and this analysis relevant to Mistie surgical and ICES surgical groups. Therefore medical patients were not included in this end point analysis.

End point values	MISTIE Surgical Management	ICES Surgical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	14		
Units: Percentage of blood clot resolved				
median (inter-quartile range (Q1-Q3))	56.7 (23.6 to 68.4)	-6.4 (-21.3 to 4.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	ICES Surgical Management v MISTIE Surgical Management
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Sign test

Notes:

[13] - Two-sided test

Statistical analysis title	Statistical Analysis 2
Comparison groups	MISTIE Surgical Management v ICES Surgical Management
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.791
Method	Sign test

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the study period	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4

Reporting groups	
Reporting group title	Medical Management
Reporting group description: -	
Reporting group title	Mistie Surgical Management
Reporting group description: -	
Reporting group title	ICES Surgical Management
Reporting group description: -	

Serious adverse events	Medical Management	Mistie Surgical Management	ICES Surgical Management
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 42 (54.76%)	28 / 54 (51.85%)	6 / 14 (42.86%)
number of deaths (all causes)	7	12	7
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Left renal mass			
subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 42 (0.00%)	0 / 54 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraoperative hemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	1 / 42 (2.38%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 42 (0.00%)	2 / 54 (3.70%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thromboembolic event			
subjects affected / exposed	3 / 42 (7.14%)	0 / 54 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	3 / 42 (7.14%)	1 / 54 (1.85%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Myocardial infarction			
subjects affected / exposed	2 / 42 (4.76%)	0 / 54 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PVC's, bigemeny			
subjects affected / exposed	0 / 42 (0.00%)	0 / 54 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 54 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Anoxic brain injury			
subjects affected / exposed	1 / 42 (2.38%)	0 / 54 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 42 (0.00%)	0 / 54 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	0 / 42 (0.00%)	3 / 54 (5.56%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Edema cerebral			
subjects affected / exposed	1 / 42 (2.38%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herniation			
subjects affected / exposed	1 / 42 (2.38%)	0 / 54 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	1 / 42 (2.38%)	0 / 54 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial hemorrhage:Catheter tract, Enlargement			
subjects affected / exposed	0 / 42 (0.00%)	0 / 54 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial hemorrhage: Catheter trace, New			
subjects affected / exposed	0 / 42 (0.00%)	0 / 54 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial hemorrhage: Tissue,			

Enlargement			
subjects affected / exposed	1 / 42 (2.38%)	4 / 54 (7.41%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial hemorrhage: Tissue, New			
subjects affected / exposed	0 / 42 (0.00%)	2 / 54 (3.70%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intracranial hemorrhage:ventricular system, Enlargement			
subjects affected / exposed	1 / 42 (2.38%)	0 / 54 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial hemorrhage: ventricular system, New			
subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial hypertension			
subjects affected / exposed	4 / 42 (9.52%)	2 / 54 (3.70%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 4	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ischemia Cerebrovascular			
subjects affected / exposed	4 / 42 (9.52%)	3 / 54 (5.56%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	2 / 42 (4.76%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnelence			
subjects affected / exposed	1 / 42 (2.38%)	0 / 54 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Stroke			
subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Syncope			
subjects affected / exposed	1 / 42 (2.38%)	0 / 54 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	2 / 42 (4.76%)	1 / 54 (1.85%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 1
Sudden death			
subjects affected / exposed	1 / 42 (2.38%)	0 / 54 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	1 / 42 (2.38%)	0 / 54 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric hemorrhage			
subjects affected / exposed	1 / 42 (2.38%)	0 / 54 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Adult respiratory distress syndrome			
subjects affected / exposed	2 / 42 (4.76%)	3 / 54 (5.56%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	1 / 42 (2.38%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 42 (2.38%)	5 / 54 (9.26%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory arrest			
subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	5 / 42 (11.90%)	6 / 54 (11.11%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 5	0 / 0
Ventilatory failure			
subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urinary retention			
subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infections and infestations			
Bacteremia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter related infection			
subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infection			
subjects affected / exposed	1 / 42 (2.38%)	0 / 54 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sepsis			
subjects affected / exposed	1 / 42 (2.38%)	3 / 54 (5.56%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Upper respiratory infection			
subjects affected / exposed	1 / 42 (2.38%)	0 / 54 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehyration			
subjects affected / exposed	0 / 42 (0.00%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Medical Management	Mistie Surgical Management	ICES Surgical Management
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 42 (57.14%)	41 / 54 (75.93%)	8 / 14 (57.14%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 42 (0.00%)	0 / 54 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 42 (9.52%)	6 / 54 (11.11%)	0 / 14 (0.00%)
occurrences (all)	4	6	0
Hypotension			
subjects affected / exposed	0 / 42 (0.00%)	3 / 54 (5.56%)	0 / 14 (0.00%)
occurrences (all)	0	5	0
Thromboembolic event			
subjects affected / exposed	1 / 42 (2.38%)	5 / 54 (9.26%)	0 / 14 (0.00%)
occurrences (all)	1	5	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 42 (4.76%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences (all)	2	1	0
Sinus bradycardia			
subjects affected / exposed	2 / 42 (4.76%)	0 / 54 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			

Intracranial hemorrhage: Catheter Tract, Enlargement			
subjects affected / exposed	0 / 42 (0.00%)	3 / 54 (5.56%)	0 / 14 (0.00%)
occurrences (all)	0	4	0
Intracranial hemorrhage: Catheter Tract, New			
subjects affected / exposed	0 / 42 (0.00%)	6 / 54 (11.11%)	0 / 14 (0.00%)
occurrences (all)	0	6	0
Intracranial hemorrhage: Tissue, Enlargement			
subjects affected / exposed	0 / 42 (0.00%)	3 / 54 (5.56%)	0 / 14 (0.00%)
occurrences (all)	0	4	0
Intracranial hemorrhage: Ventricular system, Enlargement			
subjects affected / exposed	0 / 42 (0.00%)	3 / 54 (5.56%)	0 / 14 (0.00%)
occurrences (all)	0	3	0
Seizure			
subjects affected / exposed	3 / 42 (7.14%)	4 / 54 (7.41%)	0 / 14 (0.00%)
occurrences (all)	5	4	0
Wound closure after serious fluid leak			
subjects affected / exposed	0 / 42 (0.00%)	0 / 54 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 42 (0.00%)	8 / 54 (14.81%)	0 / 14 (0.00%)
occurrences (all)	0	11	0
Leukocytosis			
subjects affected / exposed	1 / 42 (2.38%)	4 / 54 (7.41%)	0 / 14 (0.00%)
occurrences (all)	1	4	0
General disorders and administration site conditions			
Fever			
subjects affected / exposed	6 / 42 (14.29%)	13 / 54 (24.07%)	3 / 14 (21.43%)
occurrences (all)	6	14	3
HCAP			
subjects affected / exposed	0 / 42 (0.00%)	0 / 54 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Localized edema			

subjects affected / exposed	0 / 42 (0.00%)	3 / 54 (5.56%)	0 / 14 (0.00%)
occurrences (all)	0	3	0
Pain			
subjects affected / exposed	2 / 42 (4.76%)	2 / 54 (3.70%)	0 / 14 (0.00%)
occurrences (all)	2	2	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 42 (0.00%)	5 / 54 (9.26%)	1 / 14 (7.14%)
occurrences (all)	0	6	1
Diarrhoea			
subjects affected / exposed	0 / 42 (0.00%)	3 / 54 (5.56%)	0 / 14 (0.00%)
occurrences (all)	0	3	0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	5 / 42 (11.90%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences (all)	5	1	0
Atelectasis			
subjects affected / exposed	1 / 42 (2.38%)	3 / 54 (5.56%)	0 / 14 (0.00%)
occurrences (all)	1	3	0
Pleural effusion			
subjects affected / exposed	0 / 42 (0.00%)	5 / 54 (9.26%)	0 / 14 (0.00%)
occurrences (all)	0	5	0
Pneumonitis			
subjects affected / exposed	7 / 42 (16.67%)	6 / 54 (11.11%)	2 / 14 (14.29%)
occurrences (all)	7	6	2
Ventilatory failure			
subjects affected / exposed	1 / 42 (2.38%)	3 / 54 (5.56%)	0 / 14 (0.00%)
occurrences (all)	1	3	0
Renal and urinary disorders			
Acute renal failure			
subjects affected / exposed	1 / 42 (2.38%)	3 / 54 (5.56%)	0 / 14 (0.00%)
occurrences (all)	1	3	0
Hematuria			
subjects affected / exposed	2 / 42 (4.76%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences (all)	2	1	0
Urinary retention			

subjects affected / exposed	1 / 42 (2.38%)	3 / 54 (5.56%)	0 / 14 (0.00%)
occurrences (all)	1	3	0
Infections and infestations			
Lung infection			
subjects affected / exposed	2 / 42 (4.76%)	1 / 54 (1.85%)	1 / 14 (7.14%)
occurrences (all)	3	1	1
Urinary tract infection			
subjects affected / exposed	5 / 42 (11.90%)	9 / 54 (16.67%)	0 / 14 (0.00%)
occurrences (all)	6	9	0
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	1 / 42 (2.38%)	4 / 54 (7.41%)	0 / 14 (0.00%)
occurrences (all)	1	4	0
Hyperkalemia			
subjects affected / exposed	0 / 42 (0.00%)	3 / 54 (5.56%)	0 / 14 (0.00%)
occurrences (all)	0	3	0
Hypernatremia			
subjects affected / exposed	0 / 42 (0.00%)	4 / 54 (7.41%)	0 / 14 (0.00%)
occurrences (all)	0	4	0
Hypocalcemia			
subjects affected / exposed	2 / 42 (4.76%)	4 / 54 (7.41%)	0 / 14 (0.00%)
occurrences (all)	2	4	0
Hypoglycemia			
subjects affected / exposed	2 / 42 (4.76%)	1 / 54 (1.85%)	0 / 14 (0.00%)
occurrences (all)	3	1	0
Hypokalemia			
subjects affected / exposed	1 / 42 (2.38%)	6 / 54 (11.11%)	0 / 14 (0.00%)
occurrences (all)	1	6	0
Hypomagnesaemia			
subjects affected / exposed	1 / 42 (2.38%)	3 / 54 (5.56%)	0 / 14 (0.00%)
occurrences (all)	1	3	0
Hyponatremia			
subjects affected / exposed	1 / 42 (2.38%)	4 / 54 (7.41%)	0 / 14 (0.00%)
occurrences (all)	1	4	0
Hypophosphataemia			

subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	4 / 54 (7.41%) 4	0 / 14 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2009	The main changes to the protocol submitted on 12 March, 2009 relate to the addition of a new tier called Tier 3 (the ICES procedure). Tier 3 however will not be carried out in the UK or Europe (i.e. it is only to be conducted in the USA). The most important key change affecting the UK and European sites relates to a reduction in study drug dose tiers where two rt-PA doses (0.3 and 1mg) will now be tested as opposed to 3 doses (0.3, 1 and 3 mg). Since the 3mg dose is not to be used, we believe that UK and European study participants will experience less trial related risks. Additionally, there has been a change in the dosing endpoint so that rt-PA administration should continue until the residual clot is 10cc rather than 15cc (or 20% of the clot volume). The project will now run for 6 years as opposed to 4 years and each patient will be monitored for 5 days post test intervention (6 days post medical intervention) as opposed to 10 days regardless of treatment.
17 May 2009	Version 7 changes submitted on 9 April, 2009 are as follows: More detailed guidance has been developed in order to assist surgeons to place the catheters more accurately and hence improve the efficacy of clot removal. A new policy has been developed to allow placement of a second catheter where appropriate. Again, this should improve the efficacy of clot removal in certain cases. Additional follow up visits have been proposed at 9 and 12 months because preliminary data suggests that improvement can occur after the originally proposed 6 month time point. A decision has now been made to use the dose of 1mg t-PA. This has been established as the optimal dose following analysis of the preliminary stages of the trial. The exclusion criteria have been updated to conform to current practices (an INR > 1.3 is now regarded as an exclusion criteria - changed from 1.7), to include Moyamoya disease as a specific type of arteriovenous malformation that excludes potentially eligible patients. ln addition exclusion criteria that duplicated inclusion criteria were deleted. There have been a number of further small changes which are for administrative clarification only and which hence improve the clarity of the protocol from a reader's perspective.
25 February 2011	Version 7 changes submitted on 13 January 2011 are as follows: The lead Neurosurgery department location in the UK has moved: Newcastle upon Tyne Hospitals NHS Foundation Trust has moved the Neurosciences Directorate from the Newcastle General Hospital to the Royal Victoria lnfirmary. The Coordinating centre location has moved from the Newcastle General Hospital building to a University building: Neurosurgical Trials Unit, 3-4 Claremont Terrace, Newcastle upon Tyne NE2 4AE. A change of address of the site of the drug importer.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 August 2009	After stage one enrollment and DSMB review were completed, a planned protocol amendment, occurred. This specified the use of alteplase at the selected 1 mg dose (based on safety profile and clot removal efficiency), use of a surgical oversight center (based on initial surgical performance) and addition of 365 day outcome assessments. This amendment was reviewed and approved by the DSMB and executive committee. Stage two remained stratified by size, used 1:1 randomization and evaluated the safety of treatment vs. medical management.	21 December 2009

Notes:

Limitations and caveats

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

No significant limitations occurred. All limitations are summarized in the publication

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27758940

http://www.ncbi.nlm.nih.gov/pubmed/27751554