



## Clinical trial results: Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage TICH-2

### Summary

EudraCT number	2012-004108-37
Trial protocol	GB SE ES HU DK IT IE
Global end of trial date	28 February 2018

### Results information

Result version number	v1 (current)
This version publication date	18 August 2018
First version publication date	18 August 2018

### Trial information

#### Trial identification

Sponsor protocol code	12101
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#### Additional study identifiers

ISRCTN number	ISRCTN93732214
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	CTA reference: 03057/056/001/00001, REC reference: 12/EM/0369

Notes:

### Sponsors

Sponsor organisation name	University of Nottingham
Sponsor organisation address	Clinical Sciences Building, Nottingham City Campus, Hucknall Road, Nottingham, United Kingdom, NG5 1PB
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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:

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## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 December 2017
Global end of trial reached?	Yes
Global end of trial date	28 February 2018
Was the trial ended prematurely?	No

Notes:

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## General information about the trial

Main objective of the trial:

To assess whether tranexamic acid is safe and reduces death or dependency after primary intracerebral haemorrhage (PICH).

Protection of trial subjects:

Patient lacks capacity to give consent:

Lack of capacity will be determined by the participant's attending stroke physician.

If the potential participant lacked capacity to give meaningful consent (e.g. in cases of dysphasia, confusion, or reduced conscious level) the following procedures were employed:

Relatives available: If relatives were present, they were provided with brief information about the trial. Further information was provided on request. If relatives objected to the inclusion of the patient in the trial, their views were respected and the patient was not enrolled.

Full informed written consent was obtained from the patient or legal representative afterwards as soon as was practicable.

If relatives were not physically present but available and happy to speak on the telephone, the same procedure was followed. If the relative was unhappy to speak on the telephone or unable to decide, the patient was not enrolled.

Relatives not available: If no relatives were not available, a doctor was recruited, wherever possible unconnected with the trial, provide verbal information relating to the trial and obtain verbal consent for the patient's inclusion in the trial. If a doctor unconnected with the trial was not available patients were not enrolled into the trial.

If enrolled, full informed written consent was obtained from the patient or their legal representative afterwards as soon as practicable.

Serious adverse events:

Serious adverse events are common in haemorrhagic stroke, for a full list of expected SAE that are not subject to expedited reporting, please refer to Appendix ???.

As the IMP was administered once and has a short half life, serious adverse events occurring within the first 7 days were assessed for seriousness, expectedness and causality. In addition fatal SAEs and safety outcome events (VTE, recurrent stroke, TIA, MI, PAD and seizures) were reported until day 90.

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Background therapy:

Tranexamic acid is a licensed anti-fibrinolytic drug that can be administered intravenously or orally and is used in a number of bleeding conditions to reduce bleeding. In a recent mega-trial (CRASH-2) in 20,000 patients with major bleeding following trauma, tranexamic acid significantly reduced mortality, OR 0.91 (0.85-0.97), with no increase in vascular occlusive events. Treatment was most effective when given rapidly; delayed administration was associated with lack of efficacy and potential harm. In a subgroup analysis of patients with traumatic ICH, tranexamic acid showed a non-significant trend to reduced mortality, OR 0.47 (0.21-1.04), and death or dependency, OR 0.66 (0.32-1.36). However, patients in CRASH-2 were younger and had less co-morbidities than those with SICH. In another randomised controlled trial in traumatic intracerebral haemorrhage, tranexamic acid reduced death, OR 0.69 (0.35 -1.39), and death or dependency, 0.76 (0.46 - 1.27), without increased thromboembolic events.

Tranexamic acid has been tested in aneurismal subarachnoid haemorrhage, where it reduced the risk of re-bleeding at the expense of increased risk of cerebral ischaemia. However administration was for a week, conferring prolonged exposure to risk of ischaemic events.

Additionally, tranexamic acid has been found to restrict haematoma expansion in acute SICH in a small

non randomised study, although this did not report on safety. In another small study (n=156), rapid administration of a bolus of tranexamic acid within 24 hours of stroke was observed to reduce haematoma expansion (17.5% vs. 4.3%). In this study, tranexamic acid was given in combination with intensive blood pressure control, suggesting that it may be possible to combine haemostatic and haemodynamic approaches.

There have been recent calls in the literature for large clinical trials to examine the use of tranexamic acid in SICH.

Evidence for comparator:

This was a placebo-controlled trial and the placebo in this instance was 0.9% normal saline administered by intravenous infusion. The placebo was supplied, packaged, labelled, QP released and distributed as for the active IMP (tranexamic acid).

Actual start date of recruitment	01 March 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	United Kingdom: 1910
Country: Number of subjects enrolled	Denmark: 39
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Ireland: 17
Country: Number of subjects enrolled	Italy: 96
Country: Number of subjects enrolled	Malaysia: 46
Country: Number of subjects enrolled	Georgia: 141
Country: Number of subjects enrolled	Switzerland: 46
Country: Number of subjects enrolled	Turkey: 9
Worldwide total number of subjects	2325
EEA total number of subjects	2083

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)	837
From 65 to 84 years	1198
85 years and over	290

## Subject disposition

### Recruitment

#### Recruitment details:

The trial setting was in secondary care, in acute stroke services across the UK and worldwide; 2325 patients recruited from 124 centres (94 UK, 30 non-UK) in 12 countries. Participants will be recruited from the acute stroke unit or emergency admissions department. The initial approach will be from a member of the patient's usual care team.

### Pre-assignment

#### Screening details:

Inclusion criteria: Adult ( $\geq 18$  years) patients with acute SICH within 8 hours of stroke onset. (Where stroke onset time is unknown, the time of when last known well was used.

### Period 1

Period 1 title	Randomisation
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

#### Blinding implementation details:

Central randomisation using a secure internet site in real-time involved minimisation on key prognostic factors: age; sex; time since onset; systolic blood pressure; stroke severity (NIHSS); presence of intraventricular haemorrhage; & known history antiplatelet treatment used immediately prior to stroke onset - ensuring concealment of allocation, minimising differences in key baseline prognostic variables, and slightly improving statistical power

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	tranexamic acid
Arm description: active treatment	
Arm type	Experimental
Investigational medicinal product name	tranexamic acid
Investigational medicinal product code	
Other name	Cyklokapron, 100mg/ml 5ml ampoules, Pfizer Manufacturing Authorisation: PL 00057/0952)
Pharmaceutical forms	Injection, Tablet
Routes of administration	Intravenous use

#### Dosage and administration details:

Trial treatment was administered as tranexamic acid 1g (10ml in 100ml sodium chloride 0.9% infusion bag) through a venous cannula with a loading dose infusion over 10 minutes followed by 1g infusion (10ml in 250ml sodium chloride 0.9% infusion bag) over 8 hours.  
Placebo treatment replaced tranexamic acid 100mg/ml with sodium chloride 0.9%

<b>Arm title</b>	Placebo controlled
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	sodium chloride 0.9%
Investigational medicinal product code	
Other name	N/A
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

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**Dosage and administration details:**

Trial treatment was administered as a 100ml sodium chloride 0.9% infusion bag through a venous cannula over 10 minutes followed by a 250ml sodium chloride 0.9% infusion bag over 8 hours.

<b>Number of subjects in period 1</b>	tranexamic acid	Placebo controlled
Started	1161	1164
Completed	1161	1164

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**Period 2**

Period 2 title	Day 2 follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

**Blinding implementation details:**

Central randomisation using a secure internet site in real-time. Randomisation involved minimisation on key prognostic factors: age; sex; time since onset; systolic blood pressure; stroke severity (NIHSS); presence of intraventricular haemorrhage; known history antiplatelet treatment used immediately prior to stroke onset. This approach ensured concealment of allocation, minimised differences in key baseline prognostic variables, and slightly improved statistical power.

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**Arms**

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Tranexamic Acid
Arm description:	
Experimental drug	
Arm type	Experimental
Investigational medicinal product name	tranexamic acid
Investigational medicinal product code	
Other name	Cyklokapron, 100mg/ml 5ml ampoules, Pfizer Manufacturing Authorisation: PL 00057/0952)
Pharmaceutical forms	Injection, Tablet
Routes of administration	Intravenous use

**Dosage and administration details:**

Trial treatment was administered as tranexamic acid 1g (10ml in 100ml sodium chloride 0.9% infusion bag) through a venous cannula with a loading dose infusion over 10 minutes followed by 1g infusion (10ml in 250ml sodium chloride 0.9% infusion bag) over 8 hours.

Placebo treatment replaced tranexamic acid 100mg/ml with sodium chloride 0.9%

<b>Arm title</b>	Placebo
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Arm description:	
Control	
Arm type	Placebo
Investigational medicinal product name	sodium chloride 0.9%
Investigational medicinal product code	
Other name	N/A
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

**Dosage and administration details:**

Trial treatment was administered as a 100ml sodium chloride 0.9% infusion bag through a venous cannula over 10 minutes followed by a 250ml sodium chloride 0.9% infusion bag over 8 hours.

<b>Number of subjects in period 2</b>	Tranexamic Acid	Placebo
Started	1161	1164
Completed	1121	1107
Not completed	40	57
Adverse event, serious fatal	40	57

**Period 3**

Period 3 title	Day 7 follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

**Blinding implementation details:**

Central randomisation using a secure internet site in real-time. Randomisation involved minimisation on key prognostic factors: age; sex; time since onset; systolic blood pressure; stroke severity (NIHSS); presence of intraventricular haemorrhage; known history antiplatelet treatment used immediately prior to stroke onset. This approach ensured concealment of allocation, minimised differences in key baseline prognostic variables, and slightly improved statistical power.

**Arms**

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Tranexamic Acid

**Arm description:**

Experimental drug	
Arm type	Experimental
Investigational medicinal product name	tranexamic acid
Investigational medicinal product code	
Other name	Cyklokapron, 100mg/ml 5ml ampoules, Pfizer Manufacturing Authorisation: PL 00057/0952)
Pharmaceutical forms	Injection, Tablet
Routes of administration	Intravenous use

**Dosage and administration details:**

Trial treatment was administered as tranexamic acid 1g (10ml in 100ml sodium chloride 0.9% infusion

bag) through a venous cannula with a loading dose infusion over 10 minutes followed by 1g infusion (10ml in 250ml sodium chloride 0.9% infusion bag) over 8 hours.

Placebo treatment replaced tranexamic acid 100mg/ml with sodium chloride 0.9%

<b>Arm title</b>	Placebo
Arm description:	
Control	
Arm type	Placebo
Investigational medicinal product name	sodium chloride 0.9%
Investigational medicinal product code	
Other name	N/A
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Trial treatment was administered as a 100ml sodium chloride 0.9% infusion bag through a venous cannula over 10 minutes followed by a 250ml sodium chloride 0.9% infusion bag over 8 hours.

<b>Number of subjects in period 3</b>	Tranexamic Acid	Placebo
Started	1121	1107
Completed	1060	1041
Not completed	61	66
Adverse event, serious fatal	61	66

#### **Period 4**

Period 4 title	Day 90 follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Central randomisation using a secure internet site in real-time. Randomisation involved minimisation on key prognostic factors: age; sex; time since onset; systolic blood pressure; stroke severity (NIHSS); presence of intraventricular haemorrhage; known history antiplatelet treatment used immediately prior to stroke onset. This approach ensured concealment of allocation, minimised differences in key baseline prognostic variables, and slightly improved statistical power.

#### **Arms**

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Tranexamic Acid
Arm description:	
Experimental drug	
Arm type	Experimental
Investigational medicinal product name	tranexamic acid
Investigational medicinal product code	
Other name	Cyklokapron, 100mg/ml 5ml ampoules, Pfizer Manufacturing Authorisation: PL 00057/0952)
Pharmaceutical forms	Injection, Tablet
Routes of administration	Intravenous use

**Dosage and administration details:**

Trial treatment was administered as tranexamic acid 1g (10ml in 100ml sodium chloride 0.9% infusion bag) through a venous cannula with a loading dose infusion over 10 minutes followed by 1g infusion (10ml in 250ml sodium chloride 0.9% infusion bag) over 8 hours.

Placebo treatment replaced tranexamic acid 100mg/ml with sodium chloride 0.9%

<b>Arm title</b>	Placebo
Arm description:	
Control	
Arm type	Placebo
Investigational medicinal product name	tranexamic acid
Investigational medicinal product code	
Other name	Cyklokapron, 100mg/ml 5ml ampoules, Pfizer Manufacturing Authorisation: PL 00057/0952)
Pharmaceutical forms	Injection, Tablet
Routes of administration	Intravenous use

**Dosage and administration details:**

Trial treatment was administered as tranexamic acid 1g (10ml in 100ml sodium chloride 0.9% infusion bag) through a venous cannula with a loading dose infusion over 10 minutes followed by 1g infusion (10ml in 250ml sodium chloride 0.9% infusion bag) over 8 hours.

Placebo treatment replaced tranexamic acid 100mg/ml with sodium chloride 0.9%

Investigational medicinal product name	sodium chloride 0.9%
Investigational medicinal product code	
Other name	N/A
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

**Dosage and administration details:**

Trial treatment was administered as a 100ml sodium chloride 0.9% infusion bag through a venous cannula over 10 minutes followed by a 250ml sodium chloride 0.9% infusion bag over 8 hours.

<b>Number of subjects in period 4</b>	Tranexamic Acid	Placebo
Started	1060	1041
Completed	1152	1155
Not completed	158	135
Adverse event, serious fatal	149	126
Consent withdrawn by subject	6	3
Lost to follow-up	3	6
Joined	250	249



Death scores included	250	249
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## Baseline characteristics

### Reporting groups

Reporting group title	tranexamic acid
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Reporting group description:

active treatment

Reporting group title	Placebo controlled
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Reporting group description: -

Reporting group values	tranexamic acid	Placebo controlled	Total
Number of subjects	1161	1164	2325
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)	406	431	837
From 65-84 years	612	586	1198
85 years and over	143	147	290
Age continuous			
Units: years			
arithmetic mean	69.1	68.7	
standard deviation	± 13.7	± 13.9	-
Gender categorical			
Units: Subjects			
Female	519	505	1024
Male	642	659	1301

## End points

### End points reporting groups

Reporting group title	tranexamic acid
Reporting group description: active treatment	
Reporting group title	Placebo controlled
Reporting group description: -	
Reporting group title	Tranexamic Acid
Reporting group description: Experimental drug	
Reporting group title	Placebo
Reporting group description: Control	
Reporting group title	Tranexamic Acid
Reporting group description: Experimental drug	
Reporting group title	Placebo
Reporting group description: Control	
Reporting group title	Tranexamic Acid
Reporting group description: Experimental drug	
Reporting group title	Placebo
Reporting group description: Control	
Reporting group title	Tranexamic Acid
Reporting group description: Experimental drug	
Reporting group title	Placebo
Reporting group description: Control	

### Primary: Death or dependency (modified Rankin Scale, mRS) at day 90.

End point title	Death or dependency (modified Rankin Scale, mRS) at day 90.
End point description: Death or dependency (modified Rankin Scale, mRS) at day 90.	
End point type	Primary
End point timeframe: from randomisation to day 90	

End point values	Tranexamic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1152	1155		
Units: Numbers				
MRS 0	26	24		
MRS 1	115	124		
MRS 2	197	181		
MRS 3	187	194		
MRS 4	213	221		

MRS 5	164	162		
MRS 6	250	249		

### Statistical analyses

<b>Statistical analysis title</b>	Odds ratio
Comparison groups	Tranexamic Acid v Placebo
Number of subjects included in analysis	2307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	Ordinal logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.03

### Secondary: Disability (Barthel index) at day 90

End point title	Disability (Barthel index) at day 90
End point description:	Disability (Barthel index) at day 90
End point type	Secondary
End point timeframe:	from randomisation to day 90

<b>End point values</b>	Tranexamic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1152	1155		
Units: Mean				
arithmetic mean (standard deviation)	52.92 (± 44.0)	53.21 (± 43.7)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Quality of Life (EuroQol) at day 90

End point title	Quality of Life (EuroQol) at day 90
End point description: Quality of Life (EuroQol) at day 90	
End point type	Secondary
End point timeframe: from randomisation to day 90	

End point values	Tranexamic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1152	1155		
Units: Mean				
arithmetic mean (standard deviation)	0.34 (± 0.4)	0.34 (± 0.4)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Cognition

End point title	Cognition
End point description: Cognition and mood at day 90 (TICS and ZDS).	
End point type	Secondary
End point timeframe: from randomisation to day 90	

End point values	Tranexamic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1152	1155		
Units: Mean				
arithmetic mean (standard deviation)	13.57 (± 12.5)	13.94 (± 12.8)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Seizures

End point title	Seizures
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End point description:	
Seizures	
End point type	Secondary
End point timeframe:	
from randomisation to end of study	

End point values	Tranexamic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1152	1155		
Units: Numbers	77	85		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mood

End point title	Mood
End point description:	
End point type	Secondary
End point timeframe:	
Day 90	

End point values	Tranexamic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1152	1155		
Units: Mean				
arithmetic mean (standard deviation)	67.28 (± 29.5)	67.29 (± 29.9)		

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Death

End point title	Death
End point description:	
cause of death	
End point type	Other pre-specified

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End point timeframe:

from randomisation to end of study

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<b>End point values</b>	Tranexamic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1152	1155		
Units: Numbers	250	249		

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Day 90

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	1
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### Reporting groups

Reporting group title	tranexamic acid
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Reporting group description:

active treatment

Reporting group title	Placebo controlled
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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: Only serious adverse events were collected for the trial

Serious adverse events	tranexamic acid	Placebo controlled	
Total subjects affected by serious adverse events			
subjects affected / exposed	521 / 1161 (44.88%)	556 / 1164 (47.77%)	
number of deaths (all causes)	250	249	
number of deaths resulting from adverse events	250	249	
General disorders and administration site conditions			
All SAE's			
subjects affected / exposed	521 / 1161 (44.88%)	556 / 1164 (47.77%)	
occurrences causally related to treatment / all	0 / 742	5 / 781	
deaths causally related to treatment / all	0 / 250	3 / 249	

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

Non-serious adverse events	tranexamic acid	Placebo controlled	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1161 (0.00%)	0 / 1164 (0.00%)	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 December 2012	The protocol had to be amended following REC review. The changes relate to participant identifiers and the consent process for potential participants who are not able to consent for themselves and do not have relatives present.
09 October 2013	Update to Part B Section 3 (Radiation) on the REC and R&D Form.
28 February 2014	Extension to follow up period, temperature monitoring, co-enrolment. clarification of consent procedures in the emergency situation, typographical errors.
04 March 2015	addition of MRI sub study.
24 July 2015	Update to MRI sub study consent forms – to include missing initial box and remove participant signature line on personal legal representative consent form as participant would not sign this form.
09 November 2015	Minor amendment to MRI sub study consent forms.
26 May 2016	Addition of plasma biomarkers sub study in one centre.
01 September 2017	1 September 2016 - 12 month extension. Recruitment ended September 2017, grant closure February 2018.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29778325>