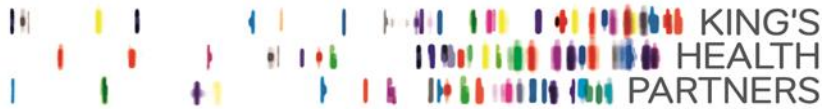

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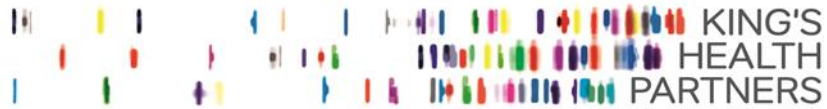
1. Project Details

Project Title*:	Evaluation of the feasibility of modulating and measuring endogenous neurogenesis with erythropoietin (rhEPO) to expedite recovery after stroke.		
NHS Contracting Organisation*:			
Project Duration*: (months)	24 months	Grant Value:	
Start Date:	01/11/2012	Agreed Extension:	
End Date:	31/05/2014	Revised End Date: (months)	N/A



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Title*:	Ms		
Surname*:	Pullen	Forename*:	Jackie
Department*:	KHPCTO,		
Role in Project*:	Co- Sponsor		
Institution*:	5		
Street*:	F16, Tower Wing, Guy's Hospital, St. Thomas Street,		
Town/City*:	London,	County*:	London
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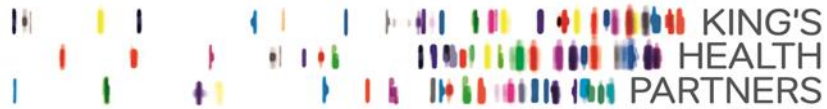
Email Address*:	jackie.pullen@kcl.ac.uk		



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3. Details of the Research Team

Co-applicant 1

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Co-applicant 2

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Role in project:	Investigator

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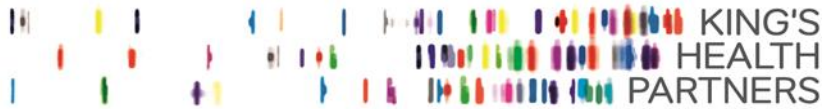
Post held:	Co-Investigator
Department:	Centre for Neuroimaging Sciences
[redacted] Organisation:	B 5 London SE5 9PJ

[redacted]

[redacted]

[redacted]



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Co-applicant 5			
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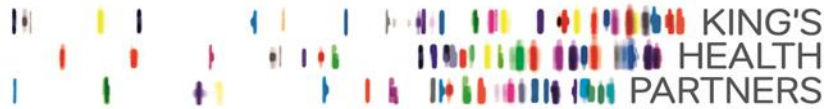
Role in project:	Investigator		

Co-applicant 6			
Title:	Dr E , A 9	8	, Ruth
Post held:	Co-Investigator		
Department:	Neuroradiology department		
Organisation:	King's College Hospital NHS Foundation Trust, London		
Telephone:	0203 299 4898		Extension:



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Role in project:	Investigator

4. CHANGES TO RESEARCH TEAM

Clinical Research Fellow addition.

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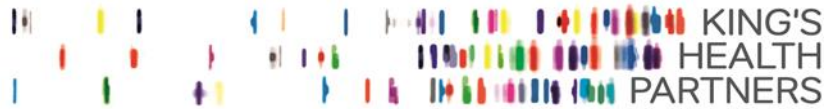
Role in project: Investigator



5. LAY/PLAIN ENGLISH SUMMARY

Stroke affects 110,000 people every year and is a common cause of adult disability. Although rehabilitation has made a significant difference, the search is on for treatments that can reduce this burden even further. Replacing cells lost in stroke is a novel physiological approach to improve recovery, especially as research shows that the human brain produces new cells throughout life and this production is increased in stroke. Furthermore, animal studies have shown that increased production of brain cells and their integration into brain circuits improves recovery in stroke and can be enhanced with drugs. One such class of drugs, recombinant human erythropoietin (rh-
available and used routinely to stimulate blood production in patients with anaemia or kidney disease. The main aim of this study is to test the principle that rh- roke.

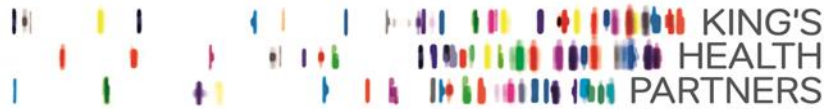
The research design was to investigate 3 groups of 30 stroke patients each who were within 48 hours of stroke onset, had not been thrombolysed and had no contraindications t treatment. All groups received the best usual treatment consisting of structured multidisciplinary
000 IU given intravenously at 1, 3
es in recovery
between the groups was assessed at 30 and 90 days after randomisation by measuring clinical recovery in function and changes in the brain perfusion and structure using magnetic resonance (MR) imaging.

The aims and objectives were to establish w rove
recovery in stroke patients who have not shown to have the potential to influence brain repair, information from the study would be used to design larger definitive clinical trials for translation into clinical use in 3-5 years.

6. KEYWORDS

Neurogenesis.
Neuroplasticity.
Spectroscopy.
Arterial Spin Labelling.

ant erythropoietin alpha)



7. SUMMARY OF RESEARCH AND FINDINGS

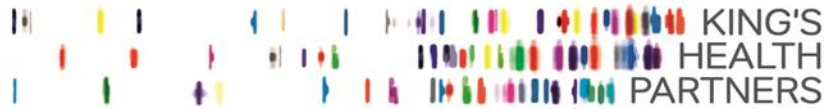
Neurogenesis and migration of new neurons into the injury site in animals can be modulated by already available growth factors such as erythropoietin (EPO). A meta-analysis of 19 animal studies showed that EPO reduced infarct size by 30% and neurobehavioral outcome improved by 40%. A small meta-analysis of growth factor interventions in stroke patients has shown a trend towards reduced dependence or death with EPO and G-CSF(granulocyte-colony stimulating factor), another growth factor known to stimulate the release of bone-marrow derived stem cells into the
neuroprotectant showed increased mortality when used concomitant with thrombolytic treatment. However, there was a trend towards improved outcomes in patients who were not thrombolysed. The hypothesis administered in the post acute phase of stroke has the potential of improving recovery in non-thrombolysed patients.

The study recruited 12 acute ischaemic stroke (AIS) patients aged between 18-85 years seen within 48 hours of onset who were not eligible for and therefore not thrombolysed. Patients were randomly allocated to routine stroke unit rehabilitation; stroke unit rehabilitation plus open label treatment wi 30)
after randomisation. We excluded patients with haematological and clotting disorders, advanced renal, hepatic or pulmonary disease, was discontinued if
the haemoglobin rose beyond > exceeds 16 g/dl in men or 14g/dL in women, blood pressure exceeds 180/110, or if there is a thrombotic event or a serious adverse event related to the trial protocol.

Key baseline clinical and imaging information was collected at the time of randomisation. Follow-up clinical data was collected on 30 days and clinical and imaging data collected at 90 days. Due to the human resource availability it was not possible to consistently have a practitioner blinded to treatment administer the follow up assessments The primary outcome measure was the Fugl-Meyer scale score measured at 90 days. Secondary clinical outcome measures were the NIHSS score, Functional Independence Measure (FIM), FIM Motor score, Modified Rankin score (MRS) and Mortality.

MR imaging and spectroscopy studies were performed with a 3.0 T GE HD.xt MRI scanner (GE Medical Systems, Milwaukee, WI, USA), using an 8-channel receive-only head coil. The scanning protocol included a 3D fast inversion-recovery prepared spoiled gradient acquisition in the steady state (IR-SPGR), with inversion time (TI) = 450 ms, echo time (TE) = 3 ms, repetition time (TR) = 7 ms, and an isotropic voxel resolution of 1 mm, used for localization of the spectroscopy voxels. The volumetric IR-SPGR images were also segmented into grey matter, white matter and CSF maps using statistical parametric to correct the spectroscopy results for partial volume CSF contamination.

Single voxel 1H MR spectra were acquired from voxels of interest positioned in the structurally intact peri-infarct thalamus (20x15 x20 mm3), the contralesional thalamus (20x15x20 mm3), and the anterior cingulate cortex (ACC, 20x20x20mm3), using a point resolved spectroscopy (PRESS) sequence with an echo time of 30 ms and a repetition time of 3 seconds. Water-scaled NAA concentrations would be derived with LCModel . The in vivo water-scaled concentrations reported by LCModel were divided by the fractional content of brain tissue (p[GM]+p[WM], where p[GM] and p[WM] represent the percentage of grey matter and white matter in the voxel, respectively) to correct for partial volume contamination of cerebrospinal fluid (CSF) in the MRS voxel. The water concentration used for water scaling was also corrected for the amount of CSF in the MRS voxel, assuming a CSF water concentration of 55.556 M.
The SVD approach assumes that the data can be represented by a Lorentzian model, which is a superposition of decayed complex sinusoids. Each sinusoid is identified by four parameters, amplitude, initial phase, frequency, and a damping factor of which the frequency and the damping factor are nonlinear parameters. This approach is adequate primarily because of the low signal-to-noise ratio (SNR) in the data and the need for high frequency resolution. Quantification of the 1.28-ppm biomarker was undertaken by measuring the amplitude/magnitude of the 1.28-ppm signal, using the unsuppressed water signal as an internal calibration standard. Relative quantification was performed by ratiometric analysis using creatine signal as a denominator. (Träber F, et al. Eur Radiol. 2006 May; Dieterle F et al. Anal Chem. 2006 Jul) Concentrations of the standard 1H brain metabolites (NAA, Lac, Creatine (Cr), Choline (Cho), myo-Insositol (mI)) would be assessed with standard Fourier-based MRS analysis methods.
The correlations would be applied between NAA, Choline, Myoinositol, Glutamine, Perfusion and the Fugl Meyer score. Spearm coefficient would be applied for the metabolites, perfusion and clinical assessment markers. Paired t test would be applied for comparison between data of NAA, Choline, Myo-inositol respectively obtained from the ipsilesional and the contralesional thalamus. ANOVA with repeated measures would be applied to assess the serial changes of NAA and their variation among patients with different clinical outcomes The results were reported as mean SD. Differences were considered significant at values of $p = 0.05$



Methods: Perfusion

Whole-brain resting cerebral perfusion images were collected with a background-suppressed, pulsed continuous arterial spin labelling (pCASL) sequence, using a 3D stack of spirals fast spin echo readout. In total 60 axial slices were collected with repetition time (TR) = 5.5 s, echo time (TE) = 25 ms, acquisition matrix = 64x64, slice thickness = 3 mm and field of view = 24 cm. The perfusion images were reconstructed with an age-appropriate perfusion template (spatial resolution: 2 x 2 x 2 mm3) was generated by first normalising th e perfusion images for each control participant to the perfusion images from one representative control participant using the FLIRT algorithm in FSL (http://www.fmrib.ox.ac.uk). A mean image was then calculated from the co-registered perfusion images for all the controls, and the perfusion images from all the patients and control subjects were normalised to this age-appropriate mean perfusion image. Finally, the mean perfusion image from the control participants was then normalised to a standard-space perfusion template, and the same transformation was applied to the perfusion images for each patient and control subject. The perfusion images were then smoothed with a 4x4x4 mm3 Gaussian smoothing kernel.

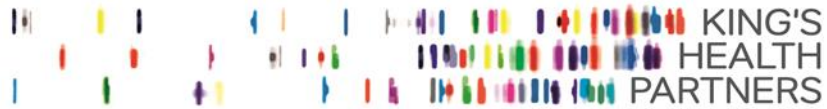
a matrix of 128x128, resulting in an effective resolution of 1.9x1.9x3 mm3

Findings:

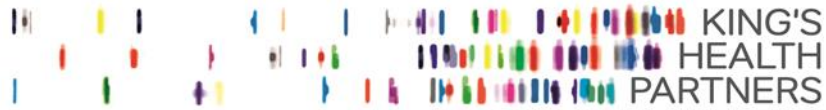
Over the course of the study period 12 patients were recruited, 10 patients were eligible and went on to randomisation 2 patients did not fulfil the inclusion criteria.

3 patients completed the protocol mandated study visits.

The findings would not be significant as the number of participants at the close of the study was well below the numbers needed to be statistically significant. The significance pre-ana>> BDC.49494949w.99F4(d 3)-9(re)dtheon ke189(to)-187(ato)-187(69(tra)5)-1p-11(e)-umb 3(het of)-18s4(ic



ID	Randomisation	Gender	DOB	Age
1	13/11/2012	M	02/07/1942	70
2	21/11/2012	F	09-Sep-73	39
3	09/01/2013	M	09/04/1965	48
4	07/02/2013	M	19/03/1946	67
5	12/03/2013	M	24/02/1966	47
6	20/03/2013	F	15/03/1937	76
7	24/06/2013	M	08/09/1967	46
8	24/06/2013	M	20/08/1969	44
9	22/08/2013	M	27/02/1976	36
10	28/08/2013	F	22/08/1956	57
11	29/08/2013	F	27/10/1963	50
12	06/03/2014	F	01/07/1932	80



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		BASELINE ASSESSMENT				VISIT 2 ASSESSMENT				VISIT 3 ASSESSMENT				baseline	visit 2	visit 3
	Treatment Allocation	NIH	Fugl.M	FIMFAM	MRS	NIH	Fugl.M	FIMFAM	MRS	NIH	Fugl.M	FIMFAM	MRS	FIM_motor_1	FIM_motor_2	FIM_motor_3
	n/a	6	36	108	4	-	-	-	-	-	-	-		54		
	LATE EPO	23	12	40	4	6	66	122	2	3	67	120	2	25	87	85
	n/a	6	74	118	2	-	-	-	-		-	-		83		
	NO TREATMENT	6	54	102	3									67		
	LATE EPO	8	45	53	4	2	92	121	1	2	94	125	1	37	90	91
	EARLY EPO	10	29	47	4									24		
	LATE EPO	2	79	124	1	0	90	123	1	0	100	125	1	89	90	91
	NO TREATMENT	7	93	123	1									91		
	EARLY EPO	6	30	79	4									47		
	EARLY EPO	9	32	78	4									43		
	EARLY EPO	7	52	121	1									86		
	LATE EPO	9	36	45	4									31		
Mean		8	48	87	3	3	83	122	1	2	87	123	1	57	89	89
Std Deviation		5.1	23.8	33.5	1.3	3.1	14.5	1.0	0.6	1.5	17.6	2.9	0.6	25.8	1.7	3.5
Median		7	41	91	4	2	90	122	1	2	94	125	1	51	90	91

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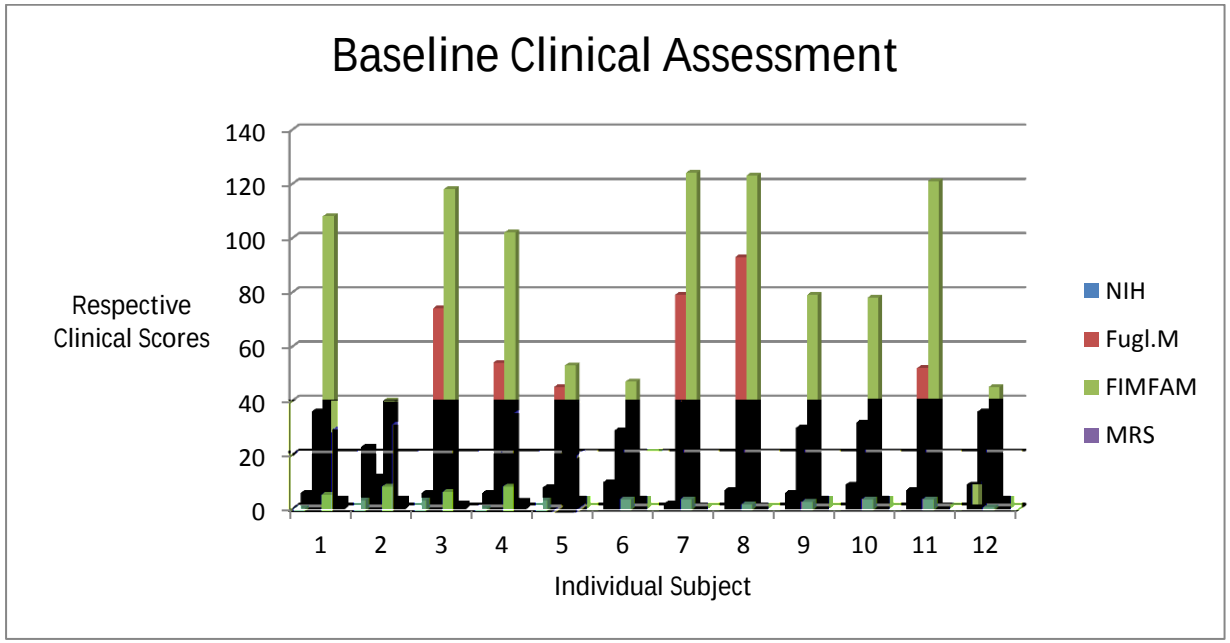
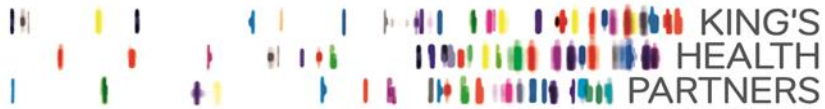
SPSS Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
NIH	12	2.00	23.00	8.2500	5.08340
FM	12	12.00	93.00	47.6667	23.83021
FIM	12	40.00	124.00	86.5000	33.46504
MRS	12	1.00	4.00	3.0000	1.34840
Valid N (listwise)	12				





8. CHANGES IN THE PROTOCOL SINCE THE INITIAL APPROVAL

Aims and objectives:
Changes to the Protocol have been amended as per the following.

Reason for Amendment
The protocol (version 1.1 10-Dec-2010) has been amended in response to REC review by NRES Committee London-Westminster.
The amended Protocol (Version 2.0 16-May-11) was approved by the REC on 26-May-11.

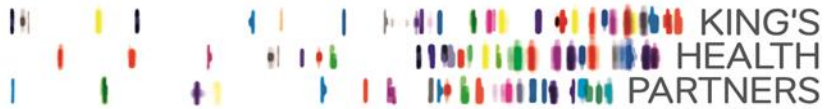
Protocol Text Amendment

Additional inclusion criterion:
Motor impairment of MRC grade 4 affecting the upper or lower limb

Delete Criterion:
NIHSS score 6-24 with NIHSS 1A (level of consciousness) score <2 at the time of enrolment.

Additional exclusion criteria amendment:
Serum creatinine >200 micromol/L

Cognitive or communication problems that limit ability to provide informed consent or follow assessment procedures
Lack of capacity as defined by the Mental Capacity Act to provide informed consent



Scientific Summary Amendment:

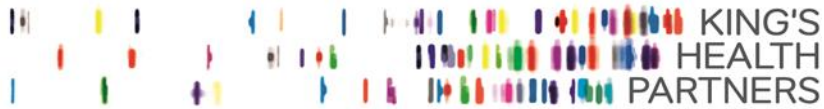
Change from: *C 0 - /6.-//. a thrombotic event or a serious adverse event related to the trial protocol.*
Change to: *C if the haemoglobin rises beyond >16 g/dl in men or 14g/dL in women, blood pressure exceeds 180/110, or if there is a thrombotic event or a serious adverse event related to the trial protocol.*

Human Studies Text Amendment:

Change from: *A more recent stu C 300 , /4 C 4 02 26 .*
Change to: *A more recent study investigated the C 300 , /4 2. . . . C 4 02 26 ptom onset.*

Additional text: *The dose of rhEPO will be 40,000 IU given intravenously and be similar to the dose used in previous studies.*

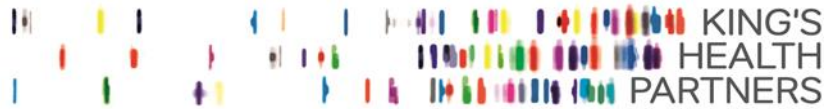
Additional text below regimen III:
Participants in the treatment arms (Regimen II and Regimen III) will be closely monitored following rhEPO infusion. Patients in hospital will be reviewed daily for blood pressure and symptoms or signs that could suggest side effects of rhEPO. Patients discharged from the hospital will be provided with an automated blood pressure monitor and asked to check their blood pressure daily. A researcher will contact the participant daily to check blood pressure readings, enquire about general health and check for symptoms of side effects of rhEPO. The researcher will arrange for the participant to be brought to the hospital if necessary. Further investigations will be performed as appropriate and patients will be managed



accordingly. Patients with side effects will be withdrawn from the study.
Hb measurements will be undertaken on day 3 and day 5 of study participation prior to the next dose of rhEPO administration in Regimen II. Rh EPO will not be given if the Hb reading exceeds 16g/dL for men and 14g/dL for women. Hb measurements will be undertaken on day 14 and day 21 of study participation prior to the next dose of rhEPO administration in Regimen III. Rh EPO will not be given if the Hb reading exceeds 16g/dL for men and 14g/dL for women
Section 9 Safety Assessment 9.1 page 23

Change from: *C* *8- Haemoglobin rises by 2g/dL*
Change to: *C*
- Haemoglobin rises by 2g/dL or exceeds > 16 g/dL (males) or > 14g/dL (females);

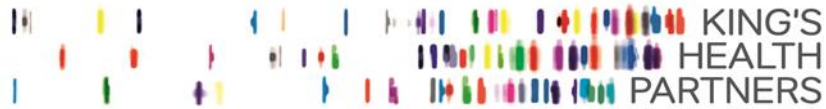
Additional text amendment:
The Data Monitoring Committee will review safety data, incidence of new thrombotic events and any cases where the Hb rises above the normal range. The data will be reviewed after 10 patients have been recruited into each of the treatment arms, or 6 monthly intervals, whichever is sooner.



PROTOCOL DEVIATION TRACKER

Subject ID	Visit	Deviation	Comment
001	1	• Patient baseline Hb level was 16.8g/dL and was included in the study, the patient was then excluded when Hb was noted to be 17.7g/dL, the inclusion criteria requires Hb to be below 16 g/dL for males. Patient eligibility amended in the CRF and patient notes- excluded as per protocol when Hb continued to rise	Patient eligibility amended excluded. Deviation and values discussed at the time with the PI who agreed no compromise to patient safety at the time or subsequently.
003	1	• Initial scan reported as showing an ischaemic lesion, but repeat scan did not demonstrate evolution of a lesion therefore no radiological evidence of a stroke and does not meet inclusion criteria	Patient eligibility amended excluded Deviation and scans discussed at the time with PI - Agreed no compromise to patient safety at the time or subsequently
004	1	• Initial CT Brain (07/02/2013) confirm deep grey matter (especially right striatal and left thalamic) mature small vessel infarcts which are consistent with a Supratentorial ischaemic stroke BUT there is no evidence of an ACUTE supratentorial ischaemic stroke. There was no clinical doubt therefore patient did not proceed to a DWI MRI for confirmation and infarct was the final diagnosis given at discharge. MRI EPO Protocol performed on 08/02/2013 There is confirmation of an established infarct on MRI which is consistent with the evolution of the infarct over time.	The protocol language is ambiguous no specific mention of lacune and acute versus established. Protocol deviation on the basis of CT evidence. Deviation and scans discussed at the time with the PI - Agreed no compromise to patient safety at the time or subsequently.
005	1	• Elevated Hb 16.8 prior to third dose of IMP, IMP administered. • Initial interpretation of the reference ranges to the lab reference ranges which are higher than the protocol stipulated values. No explanation is given for reduced reference ranges. Additionally the protocol also does not have decimal points so an exclusion criteria of >16 may have been interpreted as 17 and above rather than including decimal points in the 16 range. • Hb prior to 3rd dose of IMP on 2nd April 2013, Hb result was 16.8g/dL, this was discussed with the CI at the time and was considered clinically safe to give the final dose as the normal lab reference	Protocol deviation. Nil complications. Retrospective entry made in the notes confirming the deviation and sequence of events as discussed at the time with PI - Agreed no compromise to patient safety at the time or subsequently

		ranges had changed, the upper limit is now 16.5g/dL not 16g/dL. Post the 3rd dose, Hb was tested again and this was found to be within the normal range. Patient has since completed the study with no reported adverse events.	
005	2,3	• IMP administered with permission from local clinical team at non-study site after patient transferred off site as per clinical team decision. Sponsor not informed at the time of the deviation. Nil adverse events reported	Protocol deviation and sequence of events discussed at the time with PI - Agreed no compromise to patient safety at the time or subsequently
006	2	• MRI confirmed stroke, time reported on EPR after IMP given to patient. • IMP administered with permission from local clinical team at non-study site after patient transferred off site as per clinical team decision. Sponsor not informed at the time. Nil adverse events reported • Patient decision to not continue with trial related procedures for personal convenience, patient had moved to local hospital and therefore the logistics and inconvenience of representing to the study site was not tolerated. I had discu	Site can confirm that MRI scan was reviewed and stroke was confirmed before administration of IMP. Deviation and sequence of events discussed at the time with PI - Agreed no compromise to patient safety at the time or subsequently. Subject withdrawn from study.
007		• Discrepancy noted in timing of initial stroke onset, differing times recorded on electronic Patient Records vs paper note. The time in the paper notes records an earlier time which then moves the time past the 48 hour window for inclusion. Discussed with PI at the time and agreed late inclusion did s clinical safety. Hb level prior to the final dose of IMP was 16.10. This higher than the maximum value given in the protocol but still within the reference range for KCH lab (16.5). Subject continued on to receive the third and final dose with no complications. He has since been seen in outpatient clinic, appears to demonstrate good recovery.	Protocol deviation for inclusion timing and for Hb prior to third dosing. Nil complications. Decision taken with PI that deviation would not affect safety of the subject
009	1	• Subject was repatriated to St Mary's in Paddington on this was his local hospital and therefore the standard clinical protocol for his rehabilitation. Legal and Insurance approval was given after extensive discussions and correspondence between KCH R&D, St Mary's R&D lead, the local Stroke Consultant in charge of the patients care. The final dose of IMP was administered under St Mary's supervision with no complications or adverse effects.	



9. PATIENT AND PUBLIC INVOLVMENT

The patient population sampled were on the whole eager to engage with the consent process. Most patients and family naturally were primarily interested in whether or not the IMP had significant side effects. Potential participants were also interested to know as much as possible about the existing evidence for the efficacy of the particular.

One important area of patient and public involvement involves the follow up process. During the first visit within the hospital, trial related procedures were a lot more straightforward to implement. Once patients had left the hospital and returned home it was a lot more difficult to consistently have patients represent at the required time and sometimes at all. The follow up measures including the radiological and the clinical scores take a significant amount of time to complete rigorously. It would be helpful to further streamline the assessments in order to minimise the length of time the patients required to present for assessment both at baseline and at follow up. The length of the MRI could potentially be cut down somewhat for ease of tolerating the entire scanning process. Perhaps focusing on one modality rather than two or three may decrease the time required to complete the scanning protocol and

10. FUTURE RESEARCH REQUIRED

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