SUMMARY OF KEY POINTS: PRE-EXPERTS' MEETINGS

Professor Fenella Kirkham (Report of 16.02.12)	**Dr. Waney Squier (email of 22.02.12)**	**Professor Peter Gross (email of 19.02.12)**	**Dr. Simon Haynes (Report of 20.02.12)**	**Dr. Malcolm Coulthard (Report of 20.02.12)**
(1) Adam's background				
Developmental delay (para. 9-11 & 13)				
Adam walked at 18mths and his gross motor skills were under observation at his 4 year check,[1] which was undertaken when he was noticed to be limping on his left leg (para.9)	The cerebral cortex is not well sampled and there are no sections including insular or perisylvian cortex There is no evidence of cortical malformation in any of the cortical sections that she has examined. There is no evidence of cortical malformation in the photographs of the whole		Wishes to know Professor Kirkham's view of the significance of developmental delay, especially as to whether it could be related to any neurological disease process that may have been missed (para.7)	Any developmental delay would be attributable to him having had renal failure all his life, which had become end-stage in his pre-school years. Such problems are well known and documented. He referred to his study for 1988 – 1997, which included the unit at RBHSC run by Dr. Savage

[1] Ref: 016-098 - 18th August 1995

	fixed or unfixed brain (para.1)[2]			
Adam had mild expressive language delay in the areas of phonology and syntax (para.10)[3]				Such matters were consistent with his renal condition and clinical history (p.6)
(2) The literature				
Acute reduction in conscious level associated with cerebral oedema on neuroimaging has been reported in water intoxication in childhood (para.31)				
Arieff (1992) and Mortiz & Ayus (2005) and the Toronto papers summarised in Mortiz & Ayus do not disclose the precise nature of the hypotonic fluid given (para.32-33) Also Arieff (1992) noted that			The post-mortem findings described in Arieff's 1992 paper are the same as those discussed by Armour. The children in Arieff's study died of brain stem death caused by cerebral oedema (para.18)	Considers that the cases examined by Arieff and others are looking at different things. No one would establish a study to intentionally create a situation like Adam's – hence the absence of literature (p.8)

[2] Ref: 208-003-050 – Dr. Squier's note of 16th February 2012 in response to Professor Kirkham's queries of 15th February 2012.

[3] Ref: 016-020-042. NB. There is also a description of the way in which he chews – ie no rotator action, only up and down. We need the reference

most of the children had CNS disorders or had 'Water intoxication' (para.35)			The assertion that Arieff's patients had risk factors for CNS disorders is over-emphasised, regardless of which the inappropriate use of hypotonic IV fluids caused the injury (para.20)	He disagrees on the interpretation of the literature on the risks of infusing hypotonic fluids into children (p.8)
Recent work involving Arieff, Ayus & Moritz (2008) emphasises the role of 'additional factors' in determining the severity of cerebral oedema in women and children, particularly hypoxia (para.34)			His interpretation of Ayus & Moritz 2005 paper is that if hypotonic solutions are used there is a likelihood of causing hyponatraemia which may result in neurological injury (para.19)	
Neuroimaging was less sophisticated in the 1990s so that certain co-morbidities might not have been excluded eg: (i) predisposition to cerebral herniation; (ii) venus sinus thrombosis or PRES – in particular no neuroimaging reported for Arieff's 1992 data (para.37)			He agrees that neuroimaging is much more sophisticated now. It is a good point that Adam may have had an underlying pre-existing neurological condition (such as cerebral venous sinus thrombosis). However, there is no firm evidence of it (para.21)	
Paucity of cases in the literature of cases of cerebral oedema in children without pre-existing CNS disease				

(para.40) Apart from the 4 referred to – the cases without CNS disease had water intoxication (para.40)				
(3) Risk factors for: Chronic/Acute Venus Thrombosis				
Adam had at least 4 risk factors for chronic or acute venous thrombosis, which could have involved the cerebral venous sinus: (i) erythropoeitin; (ii) polyuric and intermittently at risk of dehydration; (iii) methyl prednisolone; (iv) jugular vein ligated and another had a CV catheter as well as; (v) anaemia secondary to iron deficiency				
(i) Erythropoietin (para.48)				
She identifies his prescriptions for erythropeitin			Adam had abnormally high haemoglobin and was prescribed erythropoietin to deal with it. He believes the	Erythropoeitin is a known risk factor for thrombosis in adults with renal failure – caused by its excessive use so

			risk relates to the high haemoglobin level (ie ploycycthaemic) as opposed to the erythropoietin (para.24)	that the haemoglobin is pushed abnormally high or is driven up to high-normal levels very rapidly (p.6) Adam was not polycythaemic (increase in red cells as a proportion of blood volume) due to excessive erythropoietin. This was not a risk factor that applied to Adam (p.6) However, he sees the issue as being linked to iron-deficiency anaemia for which erythropoietin is administered (p.6)
(ii) Polyuric and at risk of intermittent dehydration (para.48)				
Adam was polyuric and therefore intermittently at risk of dehydration			Agrees that Adam was at intermittent risk of dehydration but has seen no evidence that it happened with the frequency or severity for it to constitute a 'risk factor' (para.24)	Adam did not suffer from serious enough dehydration to induce intravascular hypovolaemia (decreased blood volume, particularly the proportion of plasma) which is a risk factor for thrombosis generally (p.6)

				The fact that Dr. Taylor had difficulty getting the line in should not necessarily be interpreted as a marker for dehydration it is not easy to canalise the central veins of young children and even experienced clinicians sometimes fail however well hydrated the child (p.7) The risk is dehydration and not polyuria and Adam was not dehydrated (p.6)
(iii) Methyl prednisolone (para.48)				
Adam was given methyl prednisolone as immunosuppression for the donor kidney during his transplant			Dilutional hyponatraemia occurred before the administration of the immunosuppressant methyl prednisolone (p.6)	If this constituted a risk factor then it might be expected to have been written up more given that methyl prednisolone is prescribed for all renal transplants – and he claims that it is not (p.7) Additionally, it is unlikely that it was a risk factor for Adam: (i) likely that he had already suffered the irreversible consequences of

				cerebral oedema before it was administered; (ii) a single dose is unlikely to have caused harm (p.7)
(iv) Ligation of left internal jugular and CV line in the neck (para.48)				
Adam may have had an internal jugular vein ligated and he had a central venous line in the neck			He agrees that a potential venous obstruction may well have been a contributory factor to the severity of the cerebral oedema (para.24)	Adam's central venous line was not obstructed because the respiratory and cardiac pressure traces were recorded (p.7)
(v) Anaemia, at least in part, secondary to iron deficiency (para.48)				
Adam had anaemia 'considered in part to be secondary to iron deficiency'. Both anaemia and iron deficiency have been associated with venous sinus thrombosis			Adam came to theatre with a haemoglobin of 10.5g/dl[4], which although is a little less than normal would not have caused high output cardiac failure assuming that it had been at a similar level throughout his life (para.5)	Adam did not have any evidence of iron deficiency anaemia and referred to the various 'markers' and test results as establishing that (p.6) The risk factors of anaemia and iron deficiency did not

[4] Ref: 093-006-017

				apply to him (p.6)
(4) Venus Sinus Thrombosis				
She makes the point that although Dr. Squier cannot find evidence for cerebral venous sinus thrombosis but does not consider that venous sinus thrombosis was excluded at the post mortem. She queries whether Dr. Anslow can exclude venous sinus thrombosis and/or subrachnoid haemorrhage from Adam's CT scan. If these conditions cannot be excluded by either Dr. Squier or Dr. Anslow[5] then she considers on the balance of probabilities they were likely to be a cause (para.48)	She states that she did not see any of the pathological features in the brain tissue usually associated with the condition.[6] She notes that it was not sought and not described at autopsy and that: "*sinus thrombosis may not be fixed and may cause secondary effects on the brain even though it is not identified at autopsy. It is not uncommon to see small intravascular thrombi in the brain at autopsy and they are constantly forming and lysing in life. It is therefore conceivable*	A cerebral venous thrombotic event during Adam's operation might/ should have fallen but instead it increased	He agrees that Adam may have had a pre-existing, unrecognised, neurological problem but that does not detract from the fact that he sustained dilutional hyponatraemia which is recognised in the literature as being lethal (eg Arieff, 1992) (para.23) Even if he had such a problem, he would not have died from it if his fluids had been properly managed (para.50)	Cerebral venous thrombosis is rare (p.5) Adam was at no greater risk of having chronic cerebral thrombosis than any other pre-school child on dialysis undergoing renal transplant (p.7) Cerebral thrombosis hypothosis has no positive support and is mere speculation (p.8)

[5] Dr. Anslow responded on 18th February 2012 that he could not exclude either venous sinus thrombosis or PRES although he found no evidence of either condition (albeit that PRES is a diagnosis best made on MRI)

[6] In her Note of 16th February 2012 in response to Professor Kirkham's queries of 15th February 2012 – Dr. Squier states that: "In cases I have examined there is usually prominent cortical vein congestion and dilation, subpial and subarachnoid bleeding and oedema or perivascular bleeding in the cortex and immediate subcortical white matter" – none of which she saw in Adam's brain.

	that sinus thrombosis could have occurred"[7] (para.50)			
(5) Effect of reduced jugular venous drainage				
She refers to the possible tying off of the internal jugular vein and the position of the central venous line catheter in the right jugular vein would have: "*reduced the opportunity for compensating for increasing cerebral oedema by drainage of blood into the jugular veins"* (para.49) Adam was likely to have had a reduction in both potential compensatory mechanisms. Namely his ability was compromised to both: (i) increase the venous drainage, and (ii) increase the re-absorption of CSF (para.55)	The prolonged obstruction of the jugular veins may be overcome by diverting flow through the paravertebral plexus (para. 49[8])		He agrees that a potential venous obstruction may well have been a contributory factor to the severity of the cerebral oedema (para.24)	Disagrees that Adam's central venous line was obstructed because respiratory and cardiac pressure traces were recorded (p.7)[9] Children like Adam will have had previous neck lines and their veins re-canalise effectively (p.7)

[7] Dr. Anslow states in his response of 18th February 2012 to Professor Kirkham's queries that: "I can see no evidence of venus thrombosis but it cannot be absolutely excluded on these images". In raising those queries, Professor Kirkham provides: "our paper which has some images".

[8] This is taken from Dr. Squier's Addendum Report dated 28th January 2012 – Ref: 206-004-050

[9] Dr. Coulthard refers in his Report of 16th February 2012 on Dr. Taylor's statement of 1st February 2012 to the statement of Dr. Dyer on 24th January 2012 in which Dr. Dyer drew attention to the fact that Dr. Taylor had said in his earlier statements that "There were both cardiac and respiratory patterns to the waveform confirming correct intravascular placement" (draft statement for the Coroner dated 30th November 1995 - Ref: 011-002-006 and Deposition to the Coroner - Ref: 011-014-099).

She considered that the first may have been compromised by the central line catheter in the right internal jugular vein, together with the likelihood of acute on chronic venous sinus thrombosis and a ligated left external jugular vein (para.55) She considered the second may have arisen through the rapid development of posterior cerebral oedema will have pushed the cerebellum down towards the foramen magnum (para.55) She also considers that the reduced jugular venous drainage would have increased the chances of increased intra cerebral venous pressure with the engorgement of the vessels with additional volume of blood, increasing contents of the skull and the intra cranial pressure – if the reserve capacity was exceeded				

(para.49)				
(6) Posterior Reversable Encephalothopy Syndrome (PRES)				
PRES may be fatal and has been described in renal disease especially after transfusion (para.50) PRES can also be associated with the development of more generalised cerebral oedema as well as white matter oedema in the posterior part of the brain and seizures – She also refers to Dr. Armour's Autopsy Report identifying *"severe white matter congestion"*[10] (para.50)	She states that she remains to be convinced that there are any reliable neuropathological grounds for making this diagnosis.[11] However she goes on: *"I know little about PRES as it is not a condition we diagnose pathologically- yet. I think it is a very interesting condition and well worth consideration"* (para.50)		Acknowledges that PRES is increasingly recognised as an entity and believes that he has come across some cases (para.25) Agrees that PRES can be considered where there is no obvious underlying cause for the cerebral oedema, but in Adam's there was such a cause – ie dilutional hyponatraemia (para.25)	PRES is simply a radiological description for acute hypertensive encephalopathy, which is something that all nephrologists need to manage very carefully in children with chronic renal failure (p3) Brain scan would not be helpful in diagnosing and controlling paediatric hypertension. So he has no experience (neither would any other neurologist) of what brains of people with that condition have looked at. Scanning the brain would

[10] Dr. Armour's Report on Autopsy – Ref: 011-010-030

[11] Dr. Anslow states in his response of 18th February 2012 to Professor Kirkham's queries that: "PRES is a diagnosis best made on MRI. All I can say is that I cannot see any low density on this CT scan to support that diagnosis"

				not improve anything (p.3) Adam did not have PRES (p.4)
(7) Adam's presentation during surgery				
Blood pressure and Seizures (para.24 & 53)				
There were no large brief increases in blood pressure or heart rate suggestive of acute seizures or Cushing responses to intracranial hypertension. It is possible that his slightly enlarged heart was not functioning quite as well as a normal heart, reducing the ability to compensate by increasing blood pressure acutely in response to seizures or intracranial pressure waves (para.24)			Adam's epidural anaesthetic might have masked to a degree any haemodynamic signs of either a Cushing response to a raised intracranial pressure or to a seizure activity (para.12) He accepts that it is likely that seizure activity occurred in Adam's brain at some point in time – as would be expected during the rapid onset of hyponatraemia (para.27)	
Adam's blood pressure rose a little during the operation[12]				

[12] Ref: 058-008-023

and substantially post-operatively.[13] It is possible that this was related to seizures but it is now impossible to prove or disprove this (para.53)				
(8) Arguments on brain death caused by dilutional hyponatraemia				
If Adam developed any primary cerebral problem – venus sinus thrombosis or PRES – he have been at risk of hyponatraemia secondary to cerebral salt wasting as well as antidiuretic hormone secretion (para.52)			If he had such an underlying problem he would have been even more susceptible to the effects of dilutional hyponatraemia (para.21) Adam's renal pathology was that his kidneys would not have been able to respond to the neuroendocrine process involved in cerebral salt wasting (para.26)	
Fall in sodium - Adam had experienced similar levels of hyponatraemia on a number of previous occasions (para.54(A))			Notes the references to similar levels of hyponatraemia, but considers it unlikely that such a rapid rate of change	

[13] Ref: 058-008-022

She also states that it is possible that the compensatory mechanisms were overwhelmed because of the rapidity of the fall in sodium but on the balance of probabilities the rapid development of fatal posterior cerebral oedema was secondary to acute on chronic cerebral venous thrombosis – probably with the additional development of posterior cerebral oedema similar to that seen in PRES			caused by large volumes of hypotonic fluids had occurred before – it is the rate of change which is significant (para.28(A))	
Generalised oedema – Adam did not have pulmonary oedema (Para.54(B))			Mechanisms of cerebral oedema and pulmonary oedema are separate. In pulmonary oedema the fluid is forced out of the circulation by hydrostatic pressure within the pulmonary capillaries into the extracellular space. Whilst diffuse cerebral oedema is caused by an osmotic gradient resulting in an excess of water in the brain cells (para.28(B))	
Massive generalised cerebral	The scan of 27.11.95 shows		He considers that Armour is	

oedema as described by Dr. Armour – There are discrepancies in brain weight which mean that it might not have been as previously assumed and that the cerebral oedema involved the posterior fossa structures more than the forebrain (para.54(C))	generalised and acute brain swelling – the hind brain is particularly swollen (para. 3.ii.a)[14] In terms of clinical significance the swelling of the hindbrain and associated compression of the brainstem is critical (para. 4vb)[15] The brain scan observations give a far more accurate reflection of the degree and distribution of swelling (para.30) Dr. Anslow reported: *"The brain has become very swollen. The CSF spaces have become obliterated and the ventricles are much smaller. These changes are severe in the posterior fossa. The cerebellar tonsils have descended through the foramen magnum."* (para.30)[16]		describing in the autopsy report severe, diffuse generalised cerebral oedema, which is not confined to the posterior structures (para.28(C))	
Apparently extensive			He disagrees with the	

[14] This is taken from Dr. Squier's Addendum Report dated 28th January 2012 – Ref: 206-004-025
[15] This is taken from Dr. Squier's Addendum Report dated 28th January 2012 – Ref: 206-004-026
[16] Report of Dr. Anslow dated 6th February 2012, para.100

literature showing fatal cerebral oedema in children who had received hypotonic fluids containing 4-5% Dextrose and 0.18-0.3% sodium chloride - reference to many of the fatal cases appear to have received 5% dextrose or to have other risk factors for developing acute cerebral oedema (para.54(D))			primary cause of cerebral oedema in Adam and whilst cerebral venous sinus thrombosis/PRES may be additional contributory factors his view is that the reason Adam developed such severe cerebral oedema was the large volume of hypotonic fluid administered IV over a short period of time (para.28(D)) He agrees that Adam's cerebral venous drainage may have been compromised making the developing cerebral oedema worse (para.28(D))	