WARWICK

MEDICAL SCHOOL

27 October 2016

Private and Confidential
Mr David Clark Horsley
Her Majesty's Coroner for Portsmouth and South East Hampshire
The Coroner's Court
1 Guildhall Square
Portsmouth
PO1 2GJ

Dear Mr Horsley

Re: HM Coroner's Regulation 28 report to prevent future deaths: University of Warwick response

I write with reference to HM Coroner's Regulation 28 report to prevent future deaths ('the report'), written following the Inquest held on 30 August 2015 into the death of Ms. Samantha Hopkins.

The report was issued on the 06 September 2016 but was not received until the 17 September 2016, with a covering letter from you dated the 16 September 2016.

I am responding on behalf of the University, but before doing so, I should like to take this opportunity to offer my sincere condolences to the family of Ms. Hopkins.

The Inquest was informed that the medical cause of Ms. Hopkins' death was subdural haematoma, and subsequently concluded that Ms. Hopkins had died due to an accident. The Coroner's Regulation 28 report raises two areas of concern with regard to Paramedic 2- The Adrenaline Trial ('Paramedic 2') and I respond to each of these below.

It is useful when reading these responses to understand the wider context of Paramedic 2, in terms both of its clinical efficacy and the gap in knowledge that it seeks to answer, namely, whether the use of adrenaline is harmful or beneficial in the context of resuscitation after a cardiac arrest. I therefore begin by providing this contextual background information:

Adrenaline became the standard NHS clinical treatment for cardiac arrest over fifty years ago, pre-dating the robust evaluation that is now required for interventions to enter into routine clinical usage. Over the past five years, a growing body of scientific evidence has questioned whether adrenaline is a safe and effective treatment in the context of resuscitation after a cardiac arrest.

This includes most recently a number of research studies which have suggested that whilst adrenaline may have a role in re-starting the heart, there is an overall reduction in post-hospital patient survival rates and an increase in the numbers of patients with severe brain damage [1].

Both the International Liaison Committee for Resuscitation (2015) and the body that sets the UK clinical guidelines for cardiac arrest, the Resuscitation Council (UK) (2015), have publicly noted the present lack of clarity around the potential harm, benefit, or benignity, of adrenaline, and have recommended that a large scale clinical trial be initiated to increase knowledge in this area [2]; [3].

Paramedic 2 is a national, five year UK trial that has been funded by the National Institute for Health Research to provide these new insights. It has been authorised for delivery in the UK by the Health Research Authority, following review by an NHS Research Ethics Committee and by the Medicine Healthcare Regulatory Agency (References: HTA 12/127/126; Oxford C REC: 14/SC/0157; EudraCT: 2014-000792-11 respectively).

I trust that this background is useful contextual information, and now turn to each of the two matters highlighted by the report as matters of concern to which the University should respond:

Coroner's matter of concern (1):
That, 'although the South Central Ambulance Service (SCAS) staff participating in the Paramedic 2 Trial had been instructed as to the classes of patients to be excluded in the trial, and information was provided inside the trial drug packet about the exclusions, they overlooked that pregnant women were expressly excluded and the exclusion warning inside the packet was also overlooked. If the exclusions had been prominently listed on the outside of the packet, this oversight might have been avoided.'
That, 'the exclusions should be prominently highlighted on the outside of the trial drug packet.'

University response:
Our response with regards to the training of SCAS staff in the inclusion and exclusion criteria of the trial, is outlined within 'matter of concern (2)' below.

With regards to the listing of exclusion criteria on the drugs packet, the present labelling complies with the relevant EU Directives 2001/20/EC, 2003/94/EC, and 91/356/EEC (inclusive of Annex 13) and has been reviewed and agreed by the Medicine Healthcare Regulatory Agency (MHRA).

Whilst there is no legal or regulatory requirement for trial exclusions to be included on the labelling of Investigational Medicinal Products (IMP), the Paramedic 2 trial team elected to go beyond these requirements and included two exclusions on the labelling, these being 'pregnant women' and 'individuals aged under 16'.

As a result of the Coroner's opinion on the matter of labelling, the University shall now include all four exclusion criteria on new labels that shall sit on the IMP bag or its external packaging. I have attached for your attention a copy of the labels that have been ordered, and which shall be distributed to all five Ambulance Services, with a direction that these must be applied to all IMP packaging, such that by January 2017, all IMP that is in circulation shall comply with this updated guidance.

The University manages the Paramedic 2 trial via our UK-CRC accredited trials unit, the Warwick Clinical Trials Unit (WCTU), which has a comprehensive Quality Management System (QMS) for the delivery and oversight of clinical trials. As part of this QMS, annual Quality Assurance visits are delivery by the WCTU at each site, and compliance with the new trial labelling requirements shall be included in these visits going forward.

Coroner's matter of concern (2):
That the Coroner was 'told in evidence that Warwick Medical School (which is responsible for the Paramedic 2 trial) had given the participating ambulance services no guidance on how the exclusions were to be highlighted to trial participants (i.e. the individual paramedics) and that this had been left to the ambulance services themselves.'

University response:
Under the Paramedic 2 training programme, the University provides training to the Principal Investigator and Research Paramedics at each of the five participating Ambulance Services. Subsequently, and under the terms of an agreed Site Agreement, each of the Sites provide training to all paramedics that shall be involved with the trial. This training specifically includes the trial inclusion and exclusion criteria.

In addition, each Principal Investigator and participating Research Paramedic receive a copy of the Study Protocol, containing written confirmation of the trial inclusion and exclusion criteria. Amendments to the trial protocol, that require additional or revised training of participating paramedics, are communicated in writing to the Principal Investigators and Research Paramedics, via email, highlighting the amendments made.

These amendments are subsequently followed by the issuing of updated instructions by the five Ambulance Services in the form of bulletins, this being in line with standard practice within the Ambulance Service.

Site adherence to the required training practices are included within the annual Quality Assurance reviews by the WCTU at each site, and the University therefore believes that a comprehensive programme of training is in place for all staff participating in Paramedic 2.

However, as a result of the Coroner's observations on this matter, the University has instructed the participating Ambulance Services that a reminder should be issued to all participating staff, to reiterate the inclusion and exclusion criteria. In order to provide additional assurance, compliance with this instruction shall be specifically audited by the WCTU during the annual Quality Assurance Site visits.

In summary, the University takes very seriously its responsibility as a Sponsor of clinical trials research, and the actions outlined in my letter demonstrate that we have very carefully considered your report, both internally and in partnership with the participating Ambulance Services.

I trust therefore that the steps we have outlined in regards to both the IMP labelling and training of participating paramedics, offer you the necessary assurances in both areas. However, please do not hesitate to contact me should you wish to discuss any element of your report, and the University's subsequent response to it, in more detail.

Yours sincerely

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