UNIVERSITY OF BIRMINGHAM

COLLEGE OF MEDICAL
AND DENTAL SCIENCES
Professor [redacted]
MD FRCP FMedSci
Pro-Vice-Chancellor
Head of College
Dean of Medicine

Confidential

Your ref: KMcL/JN/16191

Our ref: 559/DHA/JS

Kevin McLoughlin
Office of the Senior Coroner
West Yorkshire (East)
Coroner's Office and Court
71 Northgate
Wakefield
WF1 3BS

06 November 2019

Dear Mr McLoughlin

Inquest touching the death of Carl Anthony Schmidt
Response to Regulation 28 Report

Thank you for your letter of 11th September 2019 with your Regulation 28 Report and other enclosures as listed, addressed to Professor [redacted] We are also in receipt of a copy of your subsequent letter to Professor [redacted] of 10th October 2019. Please take this letter as the formal response of the University of Birmingham ('the University') to your above Report.

We do not have the contact details for Mr Schmidt's family and so have not been able to write to them to express our sadness at his death. At the outset therefore, we would be very grateful if you could pass on to them our sincere condolences. We are very conscious that as the anniversary of his death approaches, this will be a particularly difficult time for them.

Background

The University of Birmingham is committed to maintaining the highest standards of scholarly and scientific integrity in its research. It expects everyone working under the auspices of the University of Birmingham to work to these standards and clinical trials have been undertaken at and through the University for many years.

As one of the largest centres for clinical trials in the country, the University is fully committed to transparency and public accountability. It is central to our core mission to generate new knowledge through research, including working closely with healthcare providers all over the world.

One of the two clinical trials units at the University is the Cancer Research UK Clinical Trials Unit (CRCTU), which has been in existence for some 36 years and is one of the largest clinical trials units in the UK. It is a specialist research unit with remit to design, conduct, analyse, and publish investigator-led and initiated clinical trials in cancer. It aims to translate cutting-edge science into improved patient care, rapidly, and safely, through the design and conduct of large multi-centre international randomised trials as well as smaller Phase 1 trials of novel therapies.

We have outlined below the trial specific information for the 'CompARE' trial (the Trial) in relation to the trial specific ethics and integrity information, with the aim of providing assurance about participant safety and the data integrity mechanism in place for this Trial. Brief details about the aims of the Trial are also attached as **Appendix 1**.

The University is the Sponsor of this Trial which means that it is ultimately responsible for initiating, managing and financing (or arranging the financing) of the research. The Trial is run through the University's CRCTU and on a day to day basis, it is managed by Professor [redacted] as the Chief Investigator, in conjunction with the team in the CRCTU.

Cancer Research UK funded the CompARE Trial and in line with the usual funder review processes, the funder undertook an independent scientific review, where experts recommend the project for funding, as it addresses a gap in the evidence with an appropriate methodology.

Sponsor due diligence is undertaken during the trial set-up period, where trial documentation is reviewed internally by our Research Governance Team prior to submission to independent research ethics committees and regulators. In the UK, this is a national function carried out by the NHS Research Ethics Committee (REC), now operating under the Health Research Authority and the Medicines and Healthcare products Regulatory Agency (MHRA). A favourable opinion from NHS REC was received on the 27 November 2014 and regulatory MHRA approval was received on the 12 January 2015.

In addition, the University's Clinical Trials Oversight Committee (CTOC), provides oversight to all clinical trials undertaken at the University.

The Trial has a Trial Management Group (TMG), which includes co-investigators from the sites around the country that are involved in delivering the study and several head and neck medical oncology specialists and radiotherapy specialists from around the UK. The TMG meets approximately every 3 months although members are in regular contact between meetings.

The Trial also has an independent Data Monitoring Committee (DMC) – an independent group of experts established to monitor patient safety and the statistical integrity of the Trial while it is ongoing. The DMC meets every 6-12 months but also receives monthly recruitment figures. Members of the DMC are independent of the Trial, the University, and the hospital and clinician where the patient was treated. For CompARE, the DMC comprises an experienced world-leading statistician (chair), an internationally renowned head and neck radiation oncology expert and an internationally renowned head and neck surgeon.

Since the Trial opened to recruitment in July 2015, 318 patients have been recruited in numerous sites around the country, including 88 recruited into Arm 3 (dose escalated radiotherapy). Mr Schmidt signed up for the Trial in February 2018 following diagnosis for cancer of the tonsils. He was provided with the necessary Patient Information Sheet and signed the Trial consent forms for registration to the Trial and was randomised (entered into the Trial) on 20th February 2018. He received treatment under Arm 3 of the Trial between 1st March and 5th April 2018.

Action post Inquest

The CRCTU was notified of the death of Mr Schmidt by the Trial site at Leeds on 10th January 2019, who reported that the cause of death was then unknown. It is not uncommon for patients to die in cancer trials due to the life-threatening nature of the disease and, having reviewed the history provided, this was assessed in line with protocol definitions as not requiring particular exceptional action at that time.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) was submitted to MHRA on the 5th April 2019 in line with regulatory expectations, after the Sponsor was made aware of the patient's full presentation on the 29th March 2019.

The CRCTU was notified of the outcome of the subsequent inquest by the Trial site at St James' Institute of Oncology Leeds on 9th September 2019. This was a few days prior to receipt of the Regulation 28 Report dated 11th September. As the Chief Investigator, Professor [redacted] immediately reviewed the situation with CRCTU and on 12th September 2019 arranged suspension of recruitment into Arm 3 of the Trial pending further investigation being undertaken around the circumstances of the death of the patient. He notified the TMG who were in agreement and he informed the chair of the DMC. The MHRA were sent a follow up SUSAR report on 12th September and were notified of the suspension by telephone on 13th September and in writing on 16th September 2019. At the date of this Response, recruitment continues to be suspended.

Subsequent review of the Trial by the University

In the light of the outcome of the Inquest and receipt by Professor [redacted] of the Regulation 28 Report, a number of actions were undertaken to review the activity under the Trial.

a) [redacted], the clinician who treated the patient at St James' Institute of Oncology, provided both the dosage plan and the radiotherapy outlining plans (CT scans) for review.

b) The radiotherapy outlining plans and the radiotherapy doses for the patient were reviewed by the TMG, independent of [redacted] These showed that the only peripheral nerves that received the experimental higher dose were the right C5 nerve root of the brachial plexus and right recurrent laryngeal nerve. The rest of the brachial plexus on the right, and the left brachial plexus, and the cranial nerves, brain and spinal cord all received doses within the internationally accepted tolerance doses delivered by normal, routinely-used radiotherapy doses (i.e. within standard limits of radiotherapy doses used normally) and not the experimental higher dose.

c) The two pathologists who carried out the post mortem were contacted by Professor [redacted] for further information. These were [redacted] (general pathologist) and [redacted] (Consultant Neuropathologist) – copies of their correspondence are attached as **Appendix 2**. As you can see from the information provided, [redacted] the general pathologist stated that his conclusions were based on the results of [redacted] conclusions as [redacted] is not a specialist neuropathologist. As can also be seen, having received the additional information, the neuropathologist, [redacted] now considers it less likely that radiotherapy effect was the cause of patient's polyneuropathy because the experimental higher dose of radiotherapy was on the right side only but the symptoms of polyneuropathy were bilateral.

d) Following and in the light of the pathologists' input, an emergency meeting of the DMC for the Trial was convened.

The DMC (and notably the radiotherapy oncology expert) reviewed all the available information (both the dosage plan and the radiotherapy outlining plan) and did not conclude that the patient's symptoms or death were caused by direct damage from the radiotherapy on the local peripheral nerves. The reason for this is that the patient had polyneuropathy *bilaterally* including contralateral (left) arm and bilateral vocal cord palsy (i.e. including contralateral recurrent laryngeal nerve), whereas the high dose radiotherapy only affected the right recurrent laryngeal nerve and the right C5 root.

The DMC concluded that whilst the possibility of an indirect immune response due to radiotherapy cannot be completely excluded, to their knowledge, this 'abscopal' effect has only been described for tumour tissue, and not normal tissue, including neurological tissue.

Based on the information available to the DMC, it is believed that a more likely cause of death could be cisplatin neuropathy (well documented for patients receiving the standard dose of cisplatin that this patient received), alcoholic neuropathy (the patient reported drinking 120 units per week), or a virally-mediated condition such as Guillain Barre syndrome, or a combination of the above.

Conclusion

We fully appreciate that the conclusion reached at the Inquest was made on the basis of the information available to you at the time of the Inquest. However, in light of the subsequent information and review above, we hope you will agree that there are reasonable grounds to question whether the conclusion reached remains appropriate, namely that *"....on the balance of probability.....radiotherapy induced nerve injury was the likely mechanism of his death....."*. We would be grateful to know whether you consider that these are circumstances where it is appropriate to apply for a note to be added to the patient's death certificate.

The University is not aware that there have been other similar clinical outcomes to patients receiving treatment under Arm 3. Moreover, a previous study which concluded in 2015 https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-increasing-dose-radiotherapy-treat-cancer-voice-box-or-lower-part-of-the-throat-art-deco (the ART DECO study) delivered a biologically similar radiotherapy dose to that of Arm 3 of CompARE. That study recruited 276 patients and (to the best of Professor [redacted] knowledge and that of the TMG) did not result in similar adverse events. Therefore discontinuation of this treatment arm within the Trial could therefore potentially deprive future patients of the treatment afforded by the Trial.

The University has thoroughly reviewed the risk mitigation processes and operation of the Trial, the treatment provided, the potential benefit to patients, and the circumstances of this particular case. For the reasons mentioned above, the University does not believe that the experimental treatment given in Arm 3 is likely to have been the cause of death. Accordingly, and as the review has not identified reasons for continued suspension of Arm 3, the University (in consultation with the TMG and DMC) believes that resumption of recruitment into Arm 3 would be justified.

Yours sincerely

[redacted]

Professor [redacted]
Pro-Vice Chancellor
Head of College of Medical & Dental Sciences
for and on behalf of the University of Birmingham

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APPENDIX 1

CompARE Trial - Summary

Patients with intermediate-risk and high-risk oropharyngeal cancer (OPC) respond less well to the standard treatment and have a much worse outcome than low-risk OPC. New treatment paradigms are being considered for both intermediate and high-risk OPC which are more resistant to standard treatment. The purpose of the CompARE trial is to test several alternative regimens for the intensification of curative treatment for patients with intermediate-risk and high-risk OPC. These regimens involve intensifying current standard of care by the intensification of the chemotherapy or radiotherapy components or the addition of surgery or immunotherapy.

The aims of the CompARE Trial are as follows:

1. To examine the outcomes of alternative treatments aiming to improve overall survival in intermediate and high-risk OPC

2. To compare Quality of Life (QoL), toxicity outcomes and swallowing function of these alternative treatments

The CompARE Trial opened to recruitment on 6th July 2015 at the Queen Elizabeth Hospital. The first patient was randomised on 17th July 2015. Initially, three arms opened to recruitment:

Arm 1: Concomitant cisplatin chemotherapy plus radiotherapy
Concomitant chemoradiotherapy, 3-weekly cisplatin 100mg/m2 or weekly 40mg/m2 with Intensity Modulated Radiotherapy (IMRT) using 70Gy in 35F +/- neck dissection as indicated by clinical and radiological assessment 3-months post treatment. This is the international gold standard. Radiotherapy will be delivered using IMRT (70Gy in 35F) over 7 weeks to the primary tumour and lymph node metastases

Arm 2: Induction chemotherapy followed by arm 1
Induction chemotherapy (3 cycles at 3-weekly intervals: Docetaxel 75mg/m^2 + Cisplatin 80mg/m^2 + 5-Fluorouracil (5-FU) 800mg/m2/day, daily for 4 days), followed by arm 1.

Arm 3: Dose-escalated radiotherapy plus concomitant cisplatin
Dose-escalated chemoradiotherapy using intensity modulated radiotherapy (IMRT) 64Gy in 25F + Cisplatin 100mg/m^2 day 1 of week 1 and of week 5 or weekly 40mg/m^2. Neck dissection as indicated by clinical and radiological assessment at 3-months post-treatment.

Removal and addition of trial arms
Due to the multi-arm multi-stage (MAMs) design of the trial, arms can be added or removed as deemed necessary. Arm 2 closed to recruitment on 9th January 2017. Arm 4 of the trial (Resection of primary followed by arm 1) opened on 6th March 2017, but later closed on 7th February 2019.

Arm 5 opened to recruitment on 2nd October 2017.

Arm 5: Induction durvalumab plus arm 1 and then adjuvant durvalumab
One dose of induction durvalumab 1500mg by intravenous (IV) infusion followed by arm 1 within four weeks. Within one-two weeks after the completion of arm 1, durvalumab 1500mg every four weeks will be initiated for a total of 6 months.

APPENDIX 2

Correspondence from pathologists:

- [redacted] – 19 September 2019
- [redacted]19 September 2019

The Mid Yorkshire Hospitals NHS
NHS Trust

Bringing together community and hospital services

Department of Histopathology
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Tel: Hospital 0844 811 8110

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Enquiries to: [redacted]
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Our Ref: PB/RAH

19/09/2019

Professor [redacted]
Institute of Head and Neck Studies and Education
School of Cancer Sciences
University of Birmingham
Birmingham
B15 2TT

Dear Professor [redacted]

Re: Urgent Request for further information regarding CompARE Trial patient TNO 168 (inquest date 5th September 2019, West Yorkshire Coroner's Court)

Thank you for your letter, dated 19th September 2019. I am more than happy to assist you with the queries you have raised. I can confirm I performed the post-mortem examination of patient CS on the 29th November 2018. My examination did not include gross and microscopic examination of the brain and spinal cord – these were fixed and referred to [redacted] Consultant Neuropathologist at St James's University Hospital in Leeds.

This was a challenging post-mortem case, and I did hear new evidence at inquest that raised uncertainties over the mechanism of death in this case, particularly with regards to how the radiotherapy was delivered.

To address your questions in order:

The basis on which you concluded that the symptoms were caused by radiotherapy?

The history provided prior to post-mortem indicated a relatively slow progression (3-4 months) of symptoms that appeared temporally related to radiotherapy treatment. This concern was also raised clinically. I considered other causes, such as Guillain-Barre syndrome, but considered at this time that the onset of symptoms was too gradual. At inquest, further evidence indicated that it was a little more uncertain as to

how long symptoms had actually persisted for; ultimately meaning that Guillain-Barre could not be completely excluded.

[redacted] opinion was ultimately that the cause of the neurological symptoms was likely to be radiotherapy effect on local cranial and spinal nerves. As I had not found any other significant pathology to account for the symptoms I considered that this was, on the balance of probability, the most likely mechanism of death in this case.

Were there any histopathological changes in terms of necrosis, apoptosis or demyelination or any other sort in the bulbar region of the brain or in the spinal cord that would suggest damage caused by radiotherapy? Was there inflammation present?

The report from [redacted] (LA18-1277) would suggest not. I would advise approaching him for further advice in this regard, as neuropathology lies outside of my area of expertise.

Do you know if alternative causes, including Guillain-Barre, were excluded? It would be helpful to know if additional tests such as CSF analysis, EMG and nerve conduction tests were performed and considered.

Please see the comment above regarding Guillain-Barre. The hospital records indicate one CSF sample was taken. This showed clear colourless fluid, negative for culture, with white blood cells <1 x 10^6/L and red blood cells 9 x 10^6/L. I am not certain if EMG or nerve function tests were taken – I have re-reviewed the electronic clinic records and cannot find any evidence of these investigations being performed.

The outcome of the inquest was that of uncertainty and this was acknowledged in court. HM Coroner ultimately favoured radiotherapy as a contributing factor based on the temporal link between the patient's symptoms and the onset of treatment, and also based on the report provided by [redacted]

I hope this is of some use to you. Please do not hesitate to contact me if you require further information.

Yours sincerely

[redacted]

Consultant Histopathologist