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Thursday, 03 May 2018

**Private & Confidential**

Louise Ellman MP  
Labour/Co-operative Member of Parliament for Liverpool Riverside  
House of Commons  
London  
SW1A 0AA

Dear Louise

Thank you very much for writing to Great Ormond Street Hospital and I am very sorry that it has taken so long to get a response to you.

Since your letter, dated 30<sup>th</sup> November 2017, there has been 2 Medical Director before I have now substantively come into post and it also taken a couple of weeks to properly address the concerns detailed in the appendix which you wrote to Great Ormond Street Hospital with.

I am confident now we have a full response for the questions posed and I am assured as Medical Director that everything that has happened in regards to this service has been done in the right and proper way and has been subject to scrutiny.

I would gladly provide any further information which you would like to request.

I enclose a copy of the report, directly written by our tracheal team at GOSH.

If there is anything further please contact me directly.

Yours Sincerely,

Matthew Shaw



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In partnership with  
the UCL GOSH Institute of Child Health  
Patron: Her Majesty The Queen  
Chairman: Sir Michael Rake

The child first and always

**London, 07/03/2018**

To Dr Andrew Long,  
Interim Medical Director, Great Ormond Street Hospital

**Subject:** response to Ref: HoC/JEF

Dear Andrew,

We thank you for the opportunity to clarify once more the position of the clinicians at Great Ormond Street Hospital involved in the care of the 3 patients transplanted with a tissue engineering trachea. Unfortunately, we noticed that the letter from MP reports reference to a malicious website (1) which has been addressing (with racist comments) the conclusions of extensive and deep investigations conducted by University College London.

The internet blogging site ("For Better Science") is written by a German man called Leonid Schneider. Leonid Schneider has been found guilty of libel against other researchers in German courts on several occasions. From April 2017, the site has run a blog covering the writer's personal views of various tissue-engineered tracheal transplantations. The blogger uses few scientific peer-reviewed references which makes it difficult properly to comment upon it.

The circumstances and accusations have already been investigated in detail by a previous UCL-initiated formal investigation. The UCL inquiry completely vindicated GOSH a fact which needs to be used as a starting point. Nevertheless, we have distanced ourselves from Macchiarini since 2010 and have since conducted 2 transplantations without any involvement of Macchiarini or his team.

In response to the document:

**Point 1-3 Insufficient evidence:**

This is not correct. **All** data were in short supply because of the developing nature of the field. Some data may thus be defined as 'incomplete', but acellular tissue

matrices have been adopted clinically for years and have been shown to be effective in supporting cellular regeneration of different organs. Such acellular matrices have been used clinically for diaphragm and abdominal wall replacement, and for vascular patches, and as patches in the trachea. Moreover, acellular pig cardiac valves have been used successfully for number of years, without major problems.

Additionally, another leading group in the world have been using acellular matrices to regenerate skeletal muscle, SIS, which has been adopted in soldiers affected by large muscle injuries (2).

With regard to the trachea, at GOSH we were the first to adopt (for compassionate reasons) the technique in children. This was done because the child was in imminent danger of death (see Point 5 below), and was considered to be the best option at the time. Available evidence at the time from both *in vitro* and *in vivo* research had demonstrated the biocompatibility of the tissue and the capacity of the decellularised tissue, seeded with autologous stem cells, to regenerate. This technique had already been employed successfully in one adult showing efficient regeneration. The data were published in a leading journal. We used best available evidence/advice to try and save patient A. We agree that the animal experience was limited, hence our subsequent work targeted at answering unknown part of the process. We believe this represents appropriate use of bench to bedside and bedside to bench research.

**Point 4 Lack of critical expertise and background knowledge:**

The National Service for Severe Tracheal Disease in Children, based at great Ormond Street, was established in 2000 and became the sole UK recognised centre in 2006. It is the largest such service in the world and has accumulated the greatest experience. It has been peer and managerially reviewed at frequent intervals throughout its existence, and neither its experience or background knowledge have ever been the subject of criticism. It is recognised internationally, and referrals continue a year on year increase. We suggest that our relevant background experience was second to none. Further, GOSH and UCL had, and have, one of the few established regenerative medicine research teams in the country, further supporting our contention of appropriate background knowledge.

Full and appropriate ethical approval has always taken place at GOSH. The GOSH Clinical Ethics Service (CES), is a multidisciplinary group which comprises the Clinical Ethics Committee, the Rapid Response Service, and education and research roles. It holds regular ethics drop-in sessions for junior staff. The Clinical Ethics Service membership includes lay members, including a previous patient parent, an academic philosopher, bioethicists, physicians, surgeons, anaesthetists, nurses, member/s of the spiritual care team, ethicists and legal experts all of whom have qualifications and/or experience in ethical matters.

The blogger appears not to understand the difference between ethical approvals for compassionate use of medicines and those required for formal clinical trials. All appropriate permissions for the surgery we undertook were in place and were indeed **praised** by the 2017 UCL Independent Inquiry. All families refused a palliative approach, were aware that there was no guarantee of a good outcome, and that in fact we were just offering a last chance.

#### **Point 5: No immediate danger**

This is not correct. Our tracheal patients (unlike those in the Karolinska Institute in Sweden) **were** in immediate danger. The 3 patients who were treated at GOSH were all considered by both referrers and our own multi-disciplinary team to have no other practical outcome, and would have died *without* intervention. The decision was not made in isolation. We took advice about what options were available from a variety of sources nationally and internationally. The decisions were reviewed (as stated above) by our clinical ethics committees.

One other possibility which was discussed and taken in consideration was the use of homograft transplants which had previously been used as patch grafts in our unit and other centres around the world (3-4), but they had been abandoned because of a perceived risk related to bovine spongiform encephalopathy (BSE risk). Moreover, with our extensive experience, we have considered that homograft material was not really suitable for circumferential replacement.

Other alternatives such as the aortic decellularization (5) and the forearm transplants of allogeneic trachea (6) were still in their infancy and considered not suitable for our cases.

## **6. Patients and family not told**

The families and the patients (allowing for age) were carefully told of the outcomes of the use of decellularised tissue, and indeed risks were exaggerated. Note the section above describing the Ethical Approval process at GOSH.

Patient C cited in the document (Ref: HoC/JEF) was an adult who received a synthetic trachea and therefore not relevant to the therapy offered to our children. We cannot comment on this patient because at **no stage any of the GOSH team were involved in any patients receiving a synthetic trachea** and we would not currently recommend its use.

All information available regarding previous clinical experience and animal experimentation were delivered to the patients by both the clinical and the research team. The families had the opportunity to discuss the options without pressure from surgeons or scientists

## **Point 7 Marketing**

We share their view about marketing and we did not set out to market these patients. The press release was initially not planned and it was only delivered to ensure a correct story.

## **Point 8 Inaccurate reporting**

This is wrong. As far as we are aware we have been open and transparent about our clinical outcomes. As clinicians, our primary and over-riding concern is the welfare of our patients (the children) and their families. Regarding the cases performed at GOSH, 2 children are alive, but one sadly died shortly after her surgery. However, it is important to remember that ALL would have been dead *without* therapy.

Patient A's early and late clinical outcome have been widely reported (in the published literature and at scientific meetings), clearly stating the benefits and the possible difficulties related to the transplant. Despite the difficulties of publishing negative data, the outcome of patient B (who sadly died) has also been published (7). We have always been very open about our results and have highlighted the early, very significant, challenges in the care of the transplanted patients, even for patient A who has had a good long-term outcome.

*"He required 25 procedures postoperatively, mainly to clear secretions and granulation tissue (Figure 1 gives a detailed breakdown of procedures and dates). The graft itself was malacic in the initial period necessitating the insertion of two bioabsorbable tracheal stents. On four occasions during the initial period admission to the ICU was needed for respiratory support."*

CT reconstructions (figures 2 and 3: 2010-2014) show modestly narrowed segments compared native trachea at either end. There has been **no** attempt to hide the fact that these do not represent normal luminal diameters, but importantly, despite this, he lives a normal life within his personal exercise limits. Subsequent to the long term follow up, we can disclose that patient A, more than 8 years from the transplantation (done in 2010; 8), remains very well with no emergency admissions and 1-3 elective admissions for check-ups with bronchoscopy, a rate similar to that for many other patients under the GOSH tracheal team with long-term manageable mild tracheal stenoses. The patient was on the verge of death prior to his tracheal transplant in 2010. He is not only well but is now transitioning to adult care.

**In conclusion**, we strongly believe that we have always acted in the best interests of the children under the care of the tracheal team. The GOSH trachea team is one of the world's leading teams managing children with difficult airways.

The Tracheal Service at GOSH, now led by Mr. Richard Hewitt, is a group of health professionals that have been brought together specifically to provide the necessary range of expertise. The team includes specialists in ear, nose and throat (ENT), interventional radiology, intensive care, respiratory medicine, paediatric general surgery, cardiothoracic surgery and physiotherapy.

## References:

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Since it was formed in 2000 the tracheal service has become one of the largest and most successful services in Europe and a world leader in the field. Martin Elliott, Professor of Cardiothoracic Surgery, who led the team until August 2016 and led 2 out of 3 of the transplants, was the most experienced tracheal surgeon for children in the world at the time.

We have all been 'damaged' by Macchiarini's lying but we have continued to pursue a research-led approach. We have used a bedside to bench approach (10) to further understand what might or might not work.

Professor Elliott has been a public advocate about the need for transparency and reproducibility in surgical research, especially when "compassionate care' is used (11)

We have accurately reported our outcomes, however hard it was to publish negative data, because we strongly believe this is the only way to improve the approach to children with difficult airways.

#### The Aereo-Digestive Team at Great Ormond Street Hospital

Paolo De Coppi

NIHR and Nuffield Professor of Pediatric Surgery

Consultant Paediatric Surgeon

Martin Elliott

Emeritus Professor and Consultant Paediatric Cardiothoracic Surgeon

Richard Hewitt

Consultant Paediatric ENT

Nagarajan Mathiula

Consultant Paediatric Cardiothoracic Surgeon

Derek Roebuck

Consultant Paediatric Interventional Radiologist