Thank you for offering us the opportunity to respond to the submission from Professor Murray relating to the Inspire study. The Cell and Gene Therapy Catapult (CGT) takes its responsibilities for accurate submissions to Competent Authorities and Research Ethics Committees very seriously and seeks to both support and comply with the Concordat to support research integrity. There are a number of inaccuracies in Professor Murray’s submission which we wish to address.

1 Alleged inaccuracies and omissions in reporting patient outcomes in the submission to the Committee on Orphan Medicinal Products (COMP).

With respect to Patient A, Professor Murray states:

‘In the year the COMP application was submitted (2016), Patient A’s tracheal graft had completely failed, requiring it to be surgically removed together with her left lung.’

CGT made the Orphan Designation Application (ODA) in March 2016 and the information quoted in the application was derived from the latest available information published by Gonfiotti et al. 2014. The reports of Patient A’s pneumonectomy were not published until November 2016.

With respect to Patient E, the timeline submitted by CGT to COMP of Patient E’s deterioration and subsequent death was based on the information available at the time of submission.

The BBC documentary (June 2012) cited by Prof Murray stated that “two weeks after surgery” Patient E “was well enough to back to Leeds hospital”, it then went on to say that “Two weeks later Patient E “suffered a cardiac arrest during a medical procedure in Leeds”. Therefore, according to the BBC documentary Patient E died 4 weeks after surgery.

Subsequently, the Special Inquiry (September 2017) reported that Patient E ‘had been born with long segment tracheal stenosis. She had an associated cardiovascular anomaly and had undergone multiple surgeries related to this. She had previously been treated for a number of years by repeated endotracheal stenting and had been left with a permanent tracheostomy that was extremely scarred and fibrosed. She had experienced two cardiorespiratory arrests at home, related to airway compromise and both times had been resuscitated by her mother. It was these two respiratory arrests coupled with increasing difficulty in managing her permanent tracheostomy that prompted her referral from an airway team in the North of England to Great Ormond Street Hospital. Her mother and the airway team wished her to be considered for a tracheal transplant as they were certain that she was likely to die without further intervention and the local team had reached the limit of what they could offer.’

‘At operation her surgeon, Professor Martin Elliott, described the procedure as one of the most technically challenging procedures that he had ever done. It took 4 hours just to remove her native trachea such was the scarring and adherence between her native trachea and vital blood vessels.’

The Inquiry further states that: ‘Patient E was transferred to her local hospital, however within 48 -72 hours of arrival she got into difficulty and her airway was compromised. She underwent urgent bronchoscopy and her airway was found to be significantly narrowed through collapse. The local team thought that she had experienced a mediastinal bleed and that her new trachea had collapsed through extrinsic pressure. The other alternative diagnosis was that her trachea had simply collapsed with no preceding bleed. She experienced a respiratory arrest and suffered irreversible brain damage and sadly died. Her family declined a post mortem.’
Further information was also supplied in Elliott et al 2017; “the patient developed ventilatory compromise. During bronchoscopic evaluation, there had been progression of the tracheal graft narrowing. Clinicians suspected that a possible acute extrinsic compressive event had taken place (an intrathoracic haemorrhage was hypothesised). A prolonged respiratory arrest ensued, with cerebral hypoxic injury and oedema. The girl’s condition was considered irreversible at 24 hours, and she died following withdraw of ventilator support with parental consent”.

From the information available subsequent to the submission to COMP it therefore appears that Patient E died between 2 and 3 weeks after surgery, though whether due to an intrathoracic haemorrhage, primary tracheal collapse, or a combination of the two was unclear to the clinical teams looking after her.

We note that Professor Murray states the cause of death: ‘It can thus be seen that Patient E’s demise at two weeks following transplant was due to her tracheal graft failing’. These patients were not in the care of CGT Catapult and as such we do not have an opinion on the cause of death of Patient E and rely of the opinion of the specialists who looked after her.

With respect to the other patients, the submissions to the MHRA, Research Ethics Committee and COMP contained data on all available cases known to CGT Catapult and Videregen at the time. CGT was unaware of Patient C until described by the Special Inquiry in September 2017 or of the additional cases, using different technologies, described in the Leonid Schneider blog released in June 2017, though we note that the latter need to be treated with some circumspection because they have not, so far as we are aware, been subject to independent clinical publication or verification.

In summary, CGT made the relevant regulatory and ethics submissions in good faith, reporting honestly the information available to us at the time. When new information came to light, CGT voluntarily halted the trial to perform an in-depth risk assessment shared with independent key opinion leaders. This risk assessment was shared with the MHRA and resulted in CGT and Videregen voluntarily suspending the trial to allow more data to be collected. IUK have been kept informed by CGT during this time.

2 Preclinical data

The preclinical and clinical data submitted in support of the INSPIRE and TETRA trials has been reviewed by COMP, CHMP and MHRA, with recent further review with MHRA in March 2018.

3 Conclusion

The Cell and Gene Therapy Catapult (CGT) takes its responsibilities for accurate submissions to Competent Authorities and Research Ethics Committees very seriously and seeks to both support and comply with the Concordat to support research integrity. Furthermore, we have been in communication with Professor Murray by email and she was specifically made aware of our decision to formally suspend the Inspire study on the 18th March 2018.

April 2018

References