Since the Cell and Gene Therapy Catapult (CGTC) submitted their response to the Science and Technology Committee’s Research Integrity Inquiry in December 2017 (RES0033), new information has become available that raises questions about whether organisations such as the Catapult should be expected to comply with the Concordat to support research integrity.

Specific issues relating to the Inspire trial and the response of CGTC

CGTC are the sponsors for the Phase 1 Inspire trial (funded by Innovate UK) that involves the transplantation of decellularized cadaveric tracheal grafts. CGTC are collaborating with the UK SME Videregen and University College London (UCL) on both the Inspire trial and the follow-on Phase 2 trial, TETRA (funded by the EU).

1. In their response (RES0033), CGTC states: “A positive opinion on EU orphan designation for the treatment of tracheal stenosis was given by the Committee for Orphan Medicinal Products (COMP) (application number EMA/OD/069/16) and then adopted by the European Commission on 29th October 2017 (application number EU/3/16/1717)”.

The application to COMP referred to above has recently been obtained through a Freedom of Information (FOI) request from the European Medicines Agency (EMA). This is available on the ‘For Better Science’ blog along with a summary of the pertinent content. Of concern, it appears that the COMP application contains the following false claims and omissions pertaining to previous compassionate use cases. These cases have been described in UCL’s Special Inquiry into Regenerative Medicine, where they are referred to as Patients A, C, D and E. The same identification codes are used here to aid cross-referencing.

Inaccurate reporting of Patient A’s outcome. Patient A, whose case is described in a previous submission (RES0022), was transplanted with a decellularized cadaveric trachea in the Hospital Clinic Barcelona in 2008. The application to COMP states: “The patient is alive 5 years after surgery with improved and preserved lung function...”.

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.

Inaccurate reporting of Patient E’s outcome. The description of Patient E’s outcome is inaccurate, the application stating: “Initial surgery was successful however the patient suffered what is assumed to be a fatal cardiovascular event 6 weeks following surgery during a bronchoscopy procedure...”.

As highlighted in submission RES0022, Patient E, whose case was reported in a BBC documentary, was transplanted with a decellularized cadaveric trachea in Great Ormond Street Hospital on 15th February 2012. She was transferred to Leeds General Infirmary 13 days later. According to UCL’s Special Inquiry, within 48-72h of transfer, her airway became compromised, an urgent bronchoscopy showing that her trachea had collapsed. She suffered fatal brain damage and died.

It can thus be seen that Patient E’s demise at two weeks following transplant was due to her tracheal graft failing. Despite this, the trial sponsors claimed that her death occurred 6 weeks following transplant and was due to cardiovascular problems rather than to the failure of her tracheal graft.

Omissions regarding the unfavourable outcomes of other trachea transplant patients. A presentation given by a member of UCL’s trachea transplant team indicates that by 21st October 2010, an additional five adult patients had received decellularized tracheas since Patient A. The MHRA, Research Ethics Committee (REC) and COMP should have been informed of the outcomes of these patients. They are described on the ‘For Better Science’ blog and are as follows: DD, operated...
Supplementary written evidence submitted by Patricia Murray and Raphael Lévy (RES0053)

in Barcelona (graft collapsed, tracheostomy needed, graft detached, probably now deceased); **MK**, operated in Florence (mediastinitis, fistula, died within one year); **Patient C from UCL inquiry**, operated in Florence and London (graft failed, leading to a series of adverse events, died within 18 months); **GM**, operated in Florence (fistula, permanent brain damage, probably now deceased); **MM**, operated in Florence (massive bleed, died within 2 years).

A presentation by another member of the UCL team indicates that by 2014, only two out of ten patients transplanted with decellularized cadaveric tracheas had survived (these being Patient A, whose graft has since failed, and Patient D).

Furthermore, a UCL news report from 19.03.10 states: “Professor Macchiarini’s seminal work, together with the UCL team, has now saved the life of two adults and one child” 8. One of the adults referred to here is Patient A, but the other adult patient was not mentioned in UCL’s Special Inquiry, nor in the applications to MHRA, REC or COMP. There is no information about what happened to this patient after their tracheal transplant, nor where the operation was performed.

At the time the CGTC submitted their response (RES0033) to this Select Committee, they should have been aware that the application to COMP contained false information about patient outcomes. It is therefore troubling that instead of acknowledging this, the CGTC instead states the following: “CGT will review the risks and make any changes required to the trial design and/or documentation [for the Inspire trial].” “If...there are continuing concerns then the risk/benefit will be re-examined ... and further data gathered and/or a change of indication pursued if found necessary.”

Given the seriousness of the above issues (i.e., misrepresentation and omission of patient data), it is surprising that as trial sponsors, the CGTC have not considered that the best option could be to withdraw from the study and inform COMP, REC, MHRA, UCL and the funders of the two trials (Innovate UK and EU) of the reasons why.

It is not clear what further data the CGTC intend to gather to support the trial, because the COMP application reveals that no further pig studies will be undertaken (see below). Hopefully, this further data will not be obtained from additional compassionate use studies on human patients.

2. CGTC states the following in response RES0033 about The Committee for Medicinal Products for Human Use (CHMP), the EMA’s committee responsible for human medicines: “Of relevance to this Select Committee the CHMP stated that additional non-clinical studies are not required since they believed that further studies were likely to have similar outcomes and were supported by the clinical profile with case series of allografts...”

This statement by CGTC is disingenuous because it could give the impression that the pig data were supportive of the trial. This was not the case, the COMP application revealing that two pigs transplanted with decellularized tracheal scaffolds died within a short time-frame. The sponsors state the following in their application to COMP: “the study [pig study] was stopped on humane grounds”. 1

Stopping the pig study on humane grounds was the correct course of action, but surely the logical next step should be to return to bench-testing rather than proceed to human trials, especially when CGTC are now fully aware that information provided to COMP relating to the “case series of allografts” was incorrect?

A recent Science news article reports that UCL, who are supportive of the clinical trials, have indicated that ‘its researchers “have done as much as they can already to show safety and efficacy in
animals” and further animal work would be unethical’. It is difficult to see how 100% mortality in pigs is good evidence for safety and efficacy. Moreover, while most people would probably agree that undertaking additional pig studies in this case would be unethical because of the high mortality rate, surely it would be even more unethical to proceed to human trials?

**Should organisations such as the CGTC be expected to comply with the Concordat to support research integrity?**

A previous news article on the CGTC’s website indicates the following:

“The Cell Therapy Catapult was instrumental in getting Videregen from a start-up to viable business... The story has only just begun. Videregen is now on the “Innovate UK runway” with specific milestones throughout the three-year grant period that act as gateways for raising additional finance. Consequently Videregen and the UK are set to be world-leaders in trachea and bowel transplants, saving both lives and money in years to come.”

How much due diligence did the CGTC undertake before supporting Videregen and helping them to step onto the Innovate UK runway?

Now that concerns regarding the preclinical supporting data and compassionate use cases have been raised, how should the CGTC proceed?

What are CGTC’s obligations in regard to upholding good standards of research integrity?

According to the CGTC’s website, their mandate is to “catalyse and facilitate growth in the cell and gene therapy industry”. It is important that the ambition of CGTC and other organisations to achieve economic impact should not take priority over patient safety, especially when research integrity issues have already been raised.

Generating wealth should not take priority over patient health.

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**References**

5. Presentation by Prof Birchall, Sacramento State, 21st October 2010. From 38:20 https://csus.mediasite.com/Mediasite/Play/f56355d3035f4a2d96a97ae9dcde4501d

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