Further to my oral evidence to the Science and Technology Committee on 21 November 2017, I am pleased to provide further information in response to the questions posed. I wish also to highlight one further recommendation for improved practice that I did not have the opportunity to bring to the Committee’s attention.

- **Q170:** A general overview of the statistical training that UCL provides/requires at various levels (and more generally the training it provides/requires in relation to research integrity – including whether this is compulsory, and at what stage).

UCL has developed a Research Integrity Framework, which provides a route for researchers at all levels to plan training; the Framework is designed to be applicable to both staff and student research across all disciplines. [https://www.ucl.ac.uk/research/integrity/research-integrity-training-framework](https://www.ucl.ac.uk/research/integrity/research-integrity-training-framework)

The first two levels of the Framework are designed for new researchers joining UCL and cover general induction activities as well as introduction to research integrity. Levels 3 and 4 of the Framework will apply to researchers in different ways depending on the research being undertaken and the training needs of the researcher. Levels 3 and 4 cover research methods, personal skills and what we term the ‘elements of integrity’ such as research data management, research ethics, data protection, etc.

The UCL Doctoral School (which oversees doctoral education and the quality of training) runs a skills development programme for postgraduate researchers, which is informed by Vitae’s national Researcher Development Framework (RDF), a professional national development framework for planning and supporting the personal, professional and career development of researchers.

All postgraduate researchers participate in research integrity training delivered at Faculty or Departmental level. In the course of this academic year, UCL will be creating an online version of the Introduction to Research Support & Integrity workshop, which currently forms a core part of Level 2 (Introduction to Research Integrity) for postgraduate and postdoctoral researchers. The online version will help to ensure that all postgraduate researchers have access to this training, and when this is available it will then become mandatory prior to upgrade from MPhil to PhD.

With respect to statistical training, this features in levels three and four where UCL provides e-learning and in-person courses on Statistics for Researchers. More advanced statistical training is necessarily discipline specific; the relevant faculties within UCL are actively considering how statistical training can be formalised across all relevant doctoral programmes, including the potential to draw on expertise from our Statistical Science department.

- **Qq188-190:** UCL’s position on the continuation of the INSPIRE and RegenVox trials, and any participation by UCL

UCL takes very seriously its research integrity responsibilities, and for this reason, in the light of questions raised about regenerative medicine research, instigated an independent inquiry by an
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expert team of senior clinicians and scientists. The Special Inquiry into Regenerative Medicine Research (Special Inquiry) was an investigation into a range of aspects of this research area, considering patient cases, UCL’s relationship with Paolo Macchiarini, the ethical approvals for clinical trials and the fabrication of artificial trachea http://www.ucl.ac.uk/news/news-articles/0917/Special_Inquiry_Final_Report_605109702_7_.pdf. The Inquiry made a number of recommendations, all of which UCL is addressing in full. The Special Inquiry considered the RegenVOX and INSPIRE trials and reported that the appropriate ethics approval and Clinical Trial Authorisation from the MHRA were found to be in place for both trials.

Furthermore, the view of the Special Inquiry was that there are fundamental research questions and academic arguments in this field that are best served by the inclusion of patients in carefully considered, reported and monitored clinical trials and that this approach should be supported in preference to individual compassionate use cases where feasible. The Special Inquiry was satisfied that the review process for compassionate use cases in Great Ormond Street Hospital is appropriate. The Special Inquiry made specific recommendations regarding governance including compassionate use cases, however, it found no reason to hold any further separate inquiries into the historic compassionate cases.

In providing a follow-up response to this question, UCL welcomes the chance to raise the profile of the field of tissue engineering and regenerative medicine in this way. As the Committee will be aware, regenerative medicine is one of the government’s “great technologies” with substantial inward investment, the potential to transform the face of healthcare for millions of UK citizens with unmet clinical needs, and the target for a vibrant new wealth-generating industry spearheaded by around 30 SMEs and UK Big Pharma. It is therefore very timely to consider some of the matters raised in the written evidence RES0022, published on 21 November 2017.

The thrust of the case put forward in the written evidence RES0022 to the Select Committee appears to be that because there were serious problems in the applications of ethics and untried technology (very different from that of UCL and its partners) by un-monitored individuals in Sweden, then all work on tissue engineered airways should cease. The assumption appears to be that all the unfortunate characteristics of the Swedish case must apply to all those in the wider airway regenerative medicine field. We do not share this assumption. Whilst we have some concern that this particular written evidence submission RES0022 is emotive and may not be entirely factually accurate, the authors do raise some issues worthy of further exploration which we wish to address as follows.

(i) Clinical Cases

The written submission RES0022 repeats highly selected parts of the history of these patients and their treatments. These cases are covered in considerably more detail, and following extensive research from primary sources, by the Special Inquiry report. The written evidence RES0022 implies that something is being hidden or covered up about these patients, yet these cases have been subject to unusually high level of public scrutiny. Everything is in the public domain, including no less than five peer-reviewed papers, covering every aspect of their cases.
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In terms of whether or not these cases were successful, one has to note two key facts:

1. These were seriously ill patients. One was about to lose a lung (Patient A in the UCL Special Inquiry report who had a Bronchial, not Tracheal, replacement) and four (three children (Patients D, E & F in the Special Inquiry report) and one young woman (Patient C)) were about to lose their lives. Conventional therapeutic options were exhausted. There was _a priori_ evidence that the therapeutic approach adopted in each case might work at that time and full local ethics and national guidance were applied. Two (both children) of the four tracheal implants survived, and the second young woman was implanted for purely palliative reasons (to improve her quality of life and permit discharge to home) rather than curative. One child died of complications a month later, very sadly. The patient who received the bronchial replacement experienced good early airway function for a number of years but then developed a recurrence of her bronchial stenosis which required multiple stents. She underwent a left pneumonectomy in 2016, but remains alive and is reportedly in reasonable health.

2. When new technologies are being developed, it is normal for there to be a developmental period during which the clinical and scientific communities learn the best ways to apply the new treatment and learn about the potential safety and efficacy. It is rare for everything to work perfectly first time, and the introduction of tissue engineered treatments is no exception (see the histories of transplantation and gene therapy for example). However, we note again that three of five patients, including two children, are alive and well today and another was effectively palliated. This is actually a supportive case series for a new technology, but tissue engineered airway regeneration now needs to be tested formally in a clinical trial setting to scientifically test its safety and efficacy.

INSPIRE and RegenVOX represent the first such trials in the world. They are based on extensive research, including more than thirty years of published clinical and animal research evidence for INSPIRE, and additional extensive GLP (highest quality) preclinical (animal, pig) research in the case of RegenVOX. All of this work is peer-reviewed, published and in the public domain. The UCL Special Inquiry team was concerned about the accuracy of some of the evidence held by Dr Schneider and also the way that evidence was presented in the blog referenced by the written submission RES0022.

(ii) The Karolinska Reports

These again are in the public domain and we do not question their findings which have been extensively discussed. All appropriate local and national ethics, approvals and permission were in place in the UK versus none in Sweden. In the UK there was a robust, large and extensively peer-reviewed evidence base for biologic scaffolds.

(iii) Clinical Trials

Please refer to the relevant trials above: they have been approved by the MHRA and UK ethics, as well as fully supported by their sponsors, UCL, the UK Cell and Gene Therapy Catapult and the industrial partner Videregen (a UK SME). They received competitive funding from leading funding
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bodies in the UK: MRC and Innovate UK. The present technology and follow-on studies have been reviewed repeatedly and favourably by the European Medicines Agency and funded by the European Union, once again following extensive international peer-review. The trials have established extra levels of patient protection with not only independent advisory committees and data monitoring committees for both trials, but also an independent clinical multidisciplinary team review system providing a final layer of security that all patients understand the risks and benefits of the proposed treatment before they can enter the trial.

UCL can confidently say that there appear to be no trials whatsoever in the UK presently, and arguably anywhere in the world, that have greater levels of approval, oversight, governance and patient protection than INSPIRE and RegenVOX do. Stopping such approved trials, would set a seriously damaging precedent for all new treatments being introduced in the UK. Extrapolating such a move to other “high risk” clinical trials (though we argue that RegenVOX at least is in fact not at all high risk), would drive the most exciting of novel UK biomedical innovations irretrievably overseas as translation in the UK would become impossible. Should new evidence come to light that might materially impact on the likely efficacy or safety of the trials, they might then be legitimately be stopped at a future point.

Finally, as the written evidence RES0022 critically fails to point out, at the end of all this debate are seriously ill patients struggling to breathe, talk and live, frequently depending on artificial means to keep them alive. That these are rare patients does not diminish the need to find ways to give them their lives back, when all conventional treatments have failed them. In fact, most innovative therapies are initially tested in rare patient groups. Denying people the chance of participating in trials with a considerable legitimate evidence and ethical base behind them, not only takes away their hope, but also means that the world does not have a chance to see what the real potential is for tissue-engineered solutions to unmet clinical needs.

(iii) Specific Recommendations in Submission RES002

Below is UCL’s response to the specific recommendations contained in section 10 the written evidence to the Committee, RES002:

1. In accordance with the opinions of MHRA and EMA, the case for additional pig experiments is fallacious. There are no animals that are a true model for what happens in a human being and UCL scientists have done as much as they can already to show safety and efficacy in animals. The pig is not a model of human airway disease, not least because the structure of the pig trachea is substantially different to the human as it consists of contiguous cartilaginous rings and lacks the trachealis muscle sheet. Both of these differences change the biomechanics such that the outcome data are incomparable. There is already a body of evidence sufficient for large numbers of peer reviewers around the world, and the MHRA, our highly respected regulatory body in the UK, therefore, to kill more animals would not be ethical.

2. The processes and procedures around the cases performed at Great Ormond Street Hospital and University College Hospital were investigated by the Special Inquiry. All local and national ethical guidance was followed and the parents, and patient in the adult case, were fully aware of
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the risks and benefits of the intervention to which they consented. This is all fully documented. Once again we point out the differences between the Swedish problems and the ethically robust, life-saving, implants performed in London. We refer to our comments above and to the Special Inquiry.

3. Compassionate Use Guidelines exist throughout the UK. It is unethical to deny a parent the chance of their child having a potentially-life-saving treatment, tissue-engineered or otherwise, when there is substantial pre-existing evidence of efficacy, including previous children alive and well nearly 8 years after implantation, and there is no other treatment available.

4. All of UCL’s publications by Birchall et al in this area of research are fully peer-reviewed, in the public domain and as open to scrutiny and criticism as those of any other authors. All were scrutinised by the Special Inquiry and found to be robust, whilst a previous report examined some of these on an earlier occasion and also found no evidence of misconduct. The report of the Special Inquiry is publically-accessible through the UCL website.

5. As far as we are aware, only the first two patients to receive a tissue-engineered airway implant (one Bronchial, on Tracheal), and thus those with longest follow-up, received extensive media coverage. Since one was the first adult and the other the first child ever to receive a stem-cell based tissue engineered product in the world, this is possibly not surprising. It is commonplace for such world-firsts to be made public in this way. All such publicity is with the full consent of the patients and their families and is not forced on them in any way. We accept that there is a bonus to institutions and countries when “good news stories” are presented, but the primary point is that people all over the world, and of course the scientific community, take very great interest in major scientific breakthroughs of all sorts. This is not unusual, and, we would suggest, provided the privacy of the patients concerned is appropriately safeguarded, making public information about new clinical and scientific achievements is actually a very important part of public engagement with science and justification of public sector funding.

6. We are not sure what is meant in the written evidence RES0022 by the suggestion that funding bodies do not provide appropriate information to the public. In the present case, it is difficult to see how the public could obtain more information than that provided through multiple outlets. We would invite the funders to comment on this point.

7. The written evidence RES002 suggests that patients receiving treatments under existing compassionate use legislation are not protected. This is not the case; the Special Inquiry report provides a detailed consideration of the specifics as applied to the present patients. The present system is robust and engages with patients and families at every stage. Ethics committees have clear oversight. Patients are not treated as research subjects, but as patients. Most importantly, UK patients have access to potentially life-saving and/or life-transforming therapies, applied under strict governance, when their lives cannot be saved or transformed in any other known way. Moreover, these products are manufactured and supplied as medicines and thus are subject to the full pharmacovigilance of the MHRA.
8. The Special Inquiry pointed out that there is presently no standardisation of processes and procedures relating to Compassionate Use across UK hospitals and highlighted the need for a common approach. Therefore, there is a need for national conformity, based, we would argue, on the exemplary procedures at Great Ormond Street Hospital.

9. We would argue that present arrangements for regulation of Advanced Therapeutic Medicinal Products (ATMPs, a category including tissue engineering, cell and stem cell therapies, gene therapies, and others) are both stringent and appropriate.

10. There has never been greater pressure on the grants system in the UK than presently. This affects all areas of research, and apportioning priority to one area over another is a very complex matter. We are not aware of there being more grant opportunities for clinical studies in the regenerative medicine field than for preclinical and basic research.

- **Qq197-198: Whether UCL sees a need to explore further the question of patient safety** (submission referred to is here [http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/research-integrity/written/73987.pdf](http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/research-integrity/written/73987.pdf))

UCL commissioned an in-depth expert review of its regenerative medicine research, known as the Special Inquiry into Regenerative Medicine Research [http://www.ucl.ac.uk/news/news-articles/0917/Special_Inquiry_Final_Report_605109702_7_.pdf](http://www.ucl.ac.uk/news/news-articles/0917/Special_Inquiry_Final_Report_605109702_7_.pdf). The inquiry was undertaken by an independent panel five of senior scientists and Chaired by Professor Stephen Wigmore (Professor of Transplantation Surgery, University of Edinburgh).

I should have made it clear that the Special Inquiry was a thorough investigation, as recommended in the Karolinska Institute report. As explained in my oral evidence to the Select Committee, the circumstances at the Karolinska Institute were rather different to those at UCL in that the Senior Management at the Karolinska were complicit in the actions of Macchiarini, initially overturning the recommendations of the first Karolinska inquiry. UCL has acted with full transparency in its own investigation, publishing the terms of reference and the report of the Inquiry within a short time of it being finalised.

The Inquiry report notes that the field of regenerative medicine research is disputed by a number of individuals, some of whom have raised allegations of research misconduct at UCL and gave evidence to the UCL Special Inquiry. While the inquiry made a number of recommendations and revealed some serious matters for UCL to address, it did not concur with the views presented by those raising these allegations.

- **Q199: Whether UCL feels it should annotate or remove previous positive news stories about the procedures (which pre-date the investigations) such as the one at [http://www.ucl.ac.uk/news/news-articles/1008/10080601](http://www.ucl.ac.uk/news/news-articles/1008/10080601) - and more generally whether it is possible to construct a process for this which links the outcomes of misconduct processes with updates or flags on university news stories (perhaps in a similar way to retraction processes in
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journals or statements of concern). Equally, if UCL feels that it is better to maintain archived news stories as a historical record, rather than go back and amend or withdraw, then a discussion of that would be helpful.

UCL will annotate the news story with an update on the case. The patient concerned is reported on in the Special Inquiry report (referred to as Patient D). The patient remains alive and is at school; the Inquiry report and the news articles explain the patient’s condition when he underwent the surgery and the limited alternative options available to him. UCL considers that the news article was accurate at the time of its publication and that it stands as a historical record of the surgery when it was undertaken. More generally, UCL’s Media Relations team is reviewing how to handle articles when there is a subsequent significant change or evidence such as a finding of misconduct or a journal retraction. It is intended each case would be dealt with in a consistent way whereby a public record would be maintained with subsequent information included and amendments published as appropriate.

Supplementary recommendation to support the development an open communication culture amongst researchers by enabling honest errors to be declared and publication records amended

I would like to make one further suggestion to the Select Committee in addition to those that I mentioned in my oral evidence. The UUK Group on Research Integrity and/or UKRIO should be encouraged to develop recommended mechanisms for institutions to adopt in order to manage errors. There is a gap around the transparent management of genuine errors and the main process available to universities to deal with problems is their research misconduct procedure. However, a research misconduct procedure is quite a heavy handed approach and we would like researchers to be able to self-declare errors should they come to light. This will support a culture of open communication amongst researchers, especially new researchers who might be afraid to admit to errors. By having an open system to manage such declarations of errors, we could ensure that they do not spiral into something much more serious but are appropriately dealt with at an early stage, as well as make researchers feel confident that their institution will support them, and also understand that mistakes happen.

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