‘Tissue-engineered’ tracheas: an assessment of the scientific, clinical and ethical implications.

Executive summary

Clinical trials will soon be undertaken in the UK that will involve transplantation of ‘tissue-engineered’ tracheas (the ‘Inspire’ trial, funded by Innovate UK) and larynxes (the ‘RegenVox’ trial, funded by the Medical Research Council). There is much concern regarding these trials because the majority of patients who have had similar transplantations in the past have experienced adverse outcomes, the most common being death\(^1\). The extent of public interest in this story is clear from the number of comments (483) posted on a recent ‘Guardian’ article\(^2\) and by the number of signatures from members of the academic community (225) to an open letter supporting investigations about trachea transplant operations\(^3\).

In 2016, the Karolinska University Hospital (Sweden) and Landspítali University Hospital (Iceland) commissioned two investigations into trachea transplant operations conducted by the surgeon Paulo Macchiarini. A key conclusion of both investigations was that there was clear evidence of patient abuse and that the operations should not have taken place. More recently, the Swedish Central Ethics Review Board have found Macchiarini guilty of scientific misconduct and have requested the retraction of six scientific papers\(^4\).

In light of this, it is important to investigate the very first trachea transplant operation that was performed in 2008 on a young woman in Spain (Patient A), as it has played a key role in obtaining approval for the forthcoming Inspire and RegenVox trials. Patient A’s trachea transplant, which involved researchers and clinicians in the UK, was presented as a huge success story to the Science and Technology Committee in 2016 to support the case for continued government funding of regenerative medicine research. However, it now appears that Patient A’s trachea transplant operation was not so successful.

The purpose of this report is to revisit Patient A’s case along with subsequent trachea transplant operations that have taken place in the UK, focussing on the questionable ethical and scientific justifications for undertaking them, the inaccurate reporting of patient outcomes, inappropriate marketing and press statements, improper use of patients for publicity purposes, and the consequences this has had for regenerative medicine research and patient safety. Most importantly, this report recommends that the forthcoming Inspire and RegenVox trials should not take place, nor should any further ‘tissue-engineered’ tracheal or laryngeal transplants be performed in the UK on the grounds of ‘compassionate use’.

The areas that will be covered in the report are as follows:

1. Summary of Patient A’s case as reported in the Lancet in 2008
2. Immediate impact of the 2008 Lancet publication
3. Brief overview of trachea transplantation
4. Patient A’s current health status
5. Exploration of how and why a tracheal transplant was performed on Patient A
6. Exploration of why the idea of making tissue-engineered airways was so quickly accepted
7. Presentation to the Science and Technology Committee in 2016
8. UK patients that have received tracheal transplants: associated ethical and safety issues.
9. Forthcoming trials: Inspire and RegenVox
10. Recommendations
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13. Appendix: excerpt from ‘Megagrant’ by Elena Kokurina describing Patient A’s transplant

Patient A, who was living in Spain, had developed a narrowing of her left bronchus (part of the airway that leads from the trachea (windpipe) to the left lung), which was due to her previously having had tuberculosis. The narrowing had been treated by placing a stent into the bronchus to keep it open. The stent was not tolerated well by the patient, so in 2008, her clinical team decided to treat her using a new approach. This involved replacing part of her left bronchus with a cadaveric trachea (i.e., a trachea obtained from a donor after death). The donor’s cells were stripped off the cadaveric trachea using detergent and enzymes, leaving just a scaffold (tracheal frame); this was to prevent Patient A’s immune system from rejecting it. In an attempt to make the donor trachea functional, it was seeded on the inside with cells from the lining of Patient A’s own bronchus, and on the outside with ‘stem’ cells taken from her bone marrow, which were treated with growth factors to try and turn them into cartilage. The idea was that the cartilage generated from the bone marrow ‘stem’ cells would provide the structural support needed to keep the new airway open. Because the cells seeded onto the cadaveric trachea came from the patient herself, it was expected that there would not be any immune response, meaning that she would not need to take immunosuppressants. Such drugs have a number of side effects, including an increased risk of developing cancer, so being able to transplant tissues without the need for these drugs would be hugely advantageous. Patient A’s cells were allowed to grow on the donor trachea for four days in a bioreactor before being implanted. The procedure involved the collaboration of researchers and clinicians from Italy, UK and Spain. The Italian teams stripped the donor’s cells from the trachea and designed the bioreactor; the UK team prepared the cells; the Spanish-based team, led by Macchiarini, transplanted the trachea into Patient A.

Just a few months later, the procedure was reported as a huge success and was advertised in the media as the first time a windpipe had been made from stem cells. This was heralded as a major advance in medicine that could potentially solve the problems of organ shortage. Moreover, because organs generated in this way would only contain cells from the patient, there would be no need for immunosuppressants.

2. Immediate impact of the 2008 *Lancet* publication

The story caused great excitement, not only amongst the general public, but also amongst researchers, clinicians, academic institutions and funding bodies. For instance, a representative from the Medical Research Council (MRC) quickly announced increased funding for stem cell research in a Telegraph article:

“The Medical Research Council is currently encouraging proposals for collaborations to link the exciting progress in stem cell biology to clinicians working in areas where this technology can be applied”.

And an ‘impact’ statement from University College London (UCL) in 2014 indicated that the trachea transplant helped to secure “£100m government funds for regenerative medicine at the translational interface”.

Besides encouraging funding bodies to invest more money in stem cell research, especially towards the translational end (i.e., research close to clinical application), the pioneering intervention was soon being used to treat patients in Sweden, USA, Russia, Italy and UK. Some patients, like Patient A, received cadaveric tracheas, while others received synthetic airways made from a type of biocompatible plastic. Importantly, most of the patients treated after Patient A had a section of their trachea replaced, rather than a section of one of their bronchi. The reason this is important is because a patient can survive without a lung and bronchus, but they cannot survive without a trachea. The patients treated after Patient A were therefore exposed to much greater risk. Most (but not all) of the operations were performed by Paulo Macchiarini, who until 2016, was employed by the Karolinska Institute in Sweden.
3. Brief overview of trachea transplantation

It is important to understand that in contrast to organs such as the heart, kidney and liver, the trachea does not receive blood from a single ‘feed’ artery. Instead, the blood supply to the trachea is quite complex, involving numerous small vessels. This has been explained very clearly by Pierre Delaere (University Hospital Leuven, Belgium), who is an international leader in this field:

“The trachea is one of the few organs that are exceptionally difficult to transplant because of the technical difficulty to restore the blood supply to the graft. The blood supply of the 12 cm-long trachea depends in its entirety on small blood vessels branching out into numerous even smaller vessels, each of them subsequently penetrating the trachea in between the cartilage rings to provide blood supply to segments of the mucosal lining.”

Following the 2008 publication describing Patient A’s transplant, Delaere wrote to the editors of the Lancet to express his concern:

“The main drawback of the proposed reconstruction is the lack of an intrinsic blood supply to the trachea. We know that a good blood supply is the first requirement in all other tissue and organ transplantations. Therefore, the reported success of this technique is questionable.”

It can be seen therefore that right from the beginning, questions were raised about the scientific validity of this approach. The fact that the trachea that was transplanted into Patient A was not actually a living tissue, but rather just a scaffold onto which some of her cells had been seeded, made it even more difficult to see how it could possibly have worked.

4. Patient A’s current health status

In 2016, a Swedish television documentary called ‘Experimenten’ reported that Machiarini’s tracheal transplant patients were not doing very well; in fact, most of them were dead. A key finding of the documentary revealed that the tracheal transplant procedure had not previously been tested in animals. The investigation by the Karolinska University Hospital concluded that Macchiarini had not abided by the Declaration of Helsinki and his actions were in breach of medical ethics codes. Although the Swedish documentary was only concerned with patients who had been transplanted with plastic tracheas, the patients who received cadaveric tracheas by Macchiarini and/or surgeons from the UK, did not fare much better. Moreover, although most of the patients were dying, the operations were being reported as great successes in the scientific literature.

These revelations led to questions about Patient A’s pioneering operation. Had the procedure previously been tested on animals? Was she doing as well as had been reported in the scientific literature? Unfortunately, it was found that Patient A had not done so well after all and had required treatment with a stent to keep her ‘tissue-engineered’ airway open. She has since had both her ‘tissue-engineered’ airway and her left lung removed. If Patient A’s trachea rather than left bronchus had been replaced, it is possible that she would now be dead. It also appears that the procedure had not previously been tested on animals; a pig study purporting to provide proof of concept for the procedure was not published until 2010 (two years after Patient A’s operation). Moreover, the ‘tissue-engineered’ trachea was not even tested prior to surgery to see if it would accept surgical sutures (needed to attach it to the remaining part of Patient A’s windpipe).
5. Exploration of how and why a tracheal transplant was performed on Patient A

Prior to Patient A’s operation in 2008, there was no evidence from animal studies to suggest that a trachea could be generated using tissue engineering and stem cells (nor is there any plausible evidence for this today). This high-risk procedure was therefore performed without there being any scientific basis to support it, and without evidence that it would be safe or effective. This leads to the question of how approval was obtained from the Human Tissue Authority (HTA) in the UK where the stem cells and engineered trachea were produced, and how ethics approval was obtained from the Hospital Clinic Barcelona where the transplant was performed. It turns out that there was in fact no approval from the HTA to cover the preparation of the tissue-engineered trachea, which according to the lead surgeon, Macchiarini, was prepared in a veterinary lab in Bristol (see Appendix). The ethics approval had been obtained on ‘compassionate use’ grounds from the local ethics committee at the Hospital Clinic Barcelona. ‘Compassionate use’ allows an unapproved therapy to be administered outside a formal clinical trial to a patient who has a life-threatening illness, and is in accordance with Article 37 of the Declaration of Helsinki:

“In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.”

However, it is of crucial importance that Article 37 is not read out of context. For instance, Article 3 cites the Declaration of Geneva of the World Medical Association, which binds the physician with the words, “The health of my patient will be my first consideration”.

A recent report published by the Landspítali University Hospital suggests that the health of the first patient to receive a plastic trachea, Andemariam Beyene, was not the first consideration of Macchiarini and the other surgeons who were looking after him. Andemariam, who was living in Iceland, had a slow growing tumour in his trachea, and was referred to Macchiarini (based in the Karolinska University Hospital, Sweden) by his surgeon, Tomas Gudbjartsson (based in Landspítali University Hospital, Iceland). The Landspítali University Hospital investigation discovered that palliative treatment options were deliberately removed from Andemariam’s referral letter:

“Macchiarini requested from Tómas in an email, dated 12 May 2011, to change his description and evaluation of Andemariam’s medical history to put more pressure on the ethics committee. The altered text no longer mentioned laser debulking of the cancer as a viable option”.

Furthermore, no opinion was sought from an oncologist as to whether transplantation with a plastic trachea was really the best option for Andemariam. An investigation commissioned by the Karolinska University Hospital indicates that a firm diagnosis of recurrent cancer was not even obtained prior to Andemariam’s operation in 2011, which was published in the Lancet as a life-saving procedure.

A recent review article on the ethical issues surrounding compassionate use makes the following excellent point concerning the potential for patient abuse when the treating physician is also a researcher:

“Since compassionate use often combines therapeutic and research aspects, a conflict of interest might arise, for example, from a physician’s desire to “pioneer” the use of a novel intervention without paying sufficient attention to the patient’s medical needs”.

In some ways, Patient A would have been the ideal patient in which to test the pioneering ‘tissue-engineered’ airway transplant because it was her left bronchus that was diseased and not her trachea. This
meant that if the team were unable to suture the donor trachea in place, or if it had failed very quickly, then they could have simply removed the left bronchus and lung; i.e., Patient A would probably not have died even if the transplant immediately failed. If, on the other hand, a patient whose trachea needed replacing was selected as the first test case, immediate failure would have probably meant death.

It is worth noting that prior to Patient A’s procedure in 2008, the lead surgeon, Macchiarini, had pioneered another novel intervention at the Hospital Clinic Barcelona for patients with pulmonary hypertension. In brief, this involved inducing circulatory arrest while patients were under moderate, rather than deep hypothermia, the latter being the accepted best practice at that time. Macchiarini’s published outcomes were quite poor, and the novel approach was severely criticised in an editorial by a world-leader in the field, Stuart Jamieson (University of California San Diego Medical Center):

“When I was asked to write an editorial comment assessing the article published [by Macchiarini et al.] in this edition of the journal, I at first refused. There were two reasons for this. [ ] Second, I really did not believe that anybody would seriously advance the hypothesis that moderate hypothermia was as good for circulatory arrest as deeper hypothermia, and actually test this on patients”. 21

It would be a mistake, however, to ascribe all of the problems associated with the subsequent airway transplantations to Macchiarini alone. The Landspítali University Hospital investigation identified that in the case of Andemariam Beyene and the other two patients transplanted in Sweden with plastic tracheas, the ambition of the Karolinska Institute and Karolinska University Hospital to fulfil their strategic priorities was also likely to have played a major part:

“Macchiarini’s appointment to Karolinska Institutet and Karolinska University Hospital was in accordance with the strategy of these institutions to develop a centre for advanced airway surgery. It was assumed that regenerative trachea transplantations would be performed no later than three months following Macchiarini’s appointment. The centre’s structure was based on a humanitarian element involving severely ill patients from around the globe, for whom other treatment alternatives had been exhausted, thus receiving experimental treatment without perceiving these procedures as clinical trials. [. ] since the above-mentioned arrangements meant that the lives of three patients were systematically put at high risk by the strategy of the research institutions in question with regard to research in this area, the committee [appointed by the Landspítali University Hospital to assess the case of Andemariam Beyene] assesses that it cannot be ruled out that Article 2 of the European Convention on Human Rights has been violated at the Swedish institutions in question.” 16

Considering the specific case of Andemariam Beyene, the The Landspítali University Hospital report makes the following important observation:

“When Andemariam was referred to undergo treatment at Karolinska University Hospital, it had been more than half a year since Macchiarini’s appointment and he had not carried out any cutting-edge surgical procedures. According to Kjell Asplund’s report [the report commissioned by the Karolinska University Hospital], the pressure was high when the feasibility of a synthetic trachea transplant in Andemariam’s case was being evaluated.” 16

6. Exploration of why the idea of making tissue-engineered airways was so quickly accepted

It is important to ask how the idea of making ‘tissue-engineered’ airways by seeding a patient’s ‘stem’ cells on a decellularized or plastic scaffold, so quickly became accepted by major funding bodies such as the MRC, and respected universities like the Karolinska Institute, University of Bristol and UCL, without there
being any scientific evidence to support the concept. The authors of the aforementioned ‘Guardian’ article\(^2\) have suggested that the hype around stem cell research has played a big part:

>“If the sins of Karolinska have been committed elsewhere, it is partly because medical research facilities share a common milieu, which harbours common dangers. One of these is the hype surrounding stem cells. Stem cell research is a hot field of science and, according to statistics, also a rather scandal-prone one. Articles in this area are retracted 2.4 times more often than the average for biomedicine, and over half of these retractions are due to fraud. Does the “heat” of stem cell research – the high levels of funding, prestige and media coverage it enjoys – somehow encourage fraud? That’s what our experience of medical research leads us to suspect.” \(^2\)

Another key factor highlighted in this article is that the scientific community and the general public wanted to believe it:

>“Scientists can also suffer from false hope. To some extent, they believed Macchiarini because he told them what they wanted to hear. You can see this in the speed with which his “breakthroughs” were accepted. Only four months after Macchiarini operated on [Patient X], his results – provisional but very positive – were published online by the Lancet. Thereafter it was all over the news.” \(^2\)

The media have also played a big part. But while journalists should take greater care to ensure what they are reporting is accurate, in the case of the trachea transplants, most of the responsibility for inaccurate reporting lies with the scientists and clinicians themselves. The improper practice of asking patients to be interviewed and photographed by the media has been a particularly effective advertising strategy and was used to provide ‘evidence’ that the transplants were a great success, to the extent that it blinded scientists and funders alike into taking the extraordinary claims of trachea transplant researchers at face value.

### 7. Presentation to House of Commons Science and Technology Committee in 2016

In 2016, Patient A’s operation was presented as evidence to the Science and Technology Committee’s inquiry into Regenerative Medicine. It was described as a life-saving operation and as “the first successful transplant of a tissue-engineered trachea, utilising the patient’s own stem cells”\(^22,23\). However, it should be noted that there was no evidence to show that the stem cells had played any role in this transplant (see 8ii below). There was also some discussion during one of the sessions as to why the operation took place in Spain rather than the UK and whether the regulatory environment in the UK needed to be more relaxed to facilitate this sort of pioneering work. This led to the following recommendation in the published report:

>“It is important that the regulatory environment for regenerative medicine remains flexible to accommodate new and diverse approaches while also maintaining robust review processes to ensure that the most promising therapies are made available to patients. The next Government should review how regulatory ‘hospital exemptions’ are used for Advanced Therapy Medicinal Products (ATMPs) and how EU ATMP regulations might be adapted for the UK post-Brexit to reflect our own perspectives on the optimal balance between safety and accelerated access to cutting-edge technologies”. \(^23\)

In light of the events surrounding ‘tissue-engineered’ tracheas, the current Science and Technology Committee needs to reflect on the above recommendation, as a more flexible regulatory environment is unlikely to adequately safeguard patients. Regenerative medicine research is an area that needs very stringent regulation.
8. UK patients that have received tracheal transplants: associated ethical and safety issues

Patients transplanted with cadaveric or plastic tracheas either in the UK and/or with the involvement of UK surgeons have been listed in a ‘special inquiry into regenerative medicine’ commissioned by University College London (UCL)\(^24\). In the UCL report, the UK patients are indicated as A, C, D, E and F. To facilitate cross-referencing, the same letters are used here. Further particulars of the patients are presented in the UCL report, and on the ‘For Better Science’ website\(^1\). All were treated on grounds of ‘compassionate use’.

**Patient A.** Operation performed in 2008 in Hospital Clinic Barcelona, Spain, in collaboration with a UK surgeon based at the University of Bristol. Part of the patient’s left bronchus was replaced with a ‘tissue-engineered’ cadaveric trachea\(^5\). A stent was needed soon after the operation and the patient has since had her lung removed. Current status unknown. Reported as “first in human” tissue-engineered tracheal transplant\(^25\).

**Patient C.** Operation performed in 2010 in Careggi Hospital Florence, Italy, in collaboration with UK surgeons from University College London\(^1,24\). The patient’s trachea was replaced with a ‘tissue-engineered’ cadaveric trachea. The patient returned to the UK but the cadaveric trachea collapsed soon afterwards and the patient was in intensive care for 6 months. The patient then received a plastic trachea in 2011 in University College London Hospital (UCLH), UK and died four months later.

**Patient D.** Child patient (age 10). Operation performed in 2010 in Great Ormond Street Hospital, London, UK. The trachea was replaced with a ‘tissue-engineered’ cadaveric trachea\(^31\). A stent was required immediately afterwards. The patient was described as stable at four years\(^26\) but his current status is unknown. Reported as “first in child” tissue-engineered tracheal transplant\(^25\).

**Patient E.** Child patient (age 15). Operation performed in 2012 in Great Ormond Street Hospital, London, UK, and reported in a 2012 BBC documentary\(^27\). The trachea was replaced with a ‘tissue-engineered’ cadaveric trachea. The trachea collapsed after two weeks and the patient died. Despite the unfavourable outcome, the procedure was nevertheless reported as “first GMP” (Good Manufacturing Practice) tissue-engineered tracheal transplant\(^25\).

**Patient F.** Child patient (age 3). Operation performed in 2017 in Great Ormond Street Hospital, London, UK. The trachea was replaced with a ‘tissue-engineered’ cadaveric trachea. Status unknown\(^24\).

Following the revelations of research and medical misconduct highlighted in the Swedish television documentary ‘Experimenten’ (broadcast on BBC4 in October 2016 as ‘Fatal Experiments’\(^10\)), which led to the dismissal of Macchiarini from the Karolinska Institute in March 2016, the Director of the Karolinska University Hospital (KUH), Melvin Samsom, commissioned an investigation into the trachea transplantations performed by Macchiarini, a key focus being on improving patient safety\(^11\). Although University College London (UCL) has also conducted an investigation\(^24\), its main objectives were to: “report on the full facts of UCL’s involvement in regenerative medicine research”; “report on UCL’s relationship with Professor Macchiarini and the Karolinska Institute”; “review and comment on the procedures followed for ethics approvals received for UCL’s regenerative medicine research”; “review and comment on the evidence base for the use of POSS-PCU [a type of biocompatible plastic] and artificial scaffolds, taking account of data used in trials of this material”.

The KUH report, published on 31\(^{st}\) August 2016\(^11\), describes the events surrounding the transplantations and gives some insight into how these fatal operations could have taken place. The report also makes some recommendations that could prevent similar events from happening again. Although the KUH investigation was centred on three patients who received plastic, rather than cadaveric tracheas, it should be noted that the outcomes for all patients have been extremely poor, irrespective of what the tracheas were made of\(^1\).
It appears that many of the shortcomings identified in the Swedish report also apply to tracheal transplants performed previously in the UK under compassionate use, and to the forthcoming airway transplantation trials that will soon take place at UCL, namely, the ‘Inspire’ and ‘RegenVox’ trials that will transplant tissue-engineered tracheas (windpipes) and larynxes (voiceboxes), respectively. The Inspire trial aims to recruit four adult patients, and the RegenVox trial aims to recruit ten patients.

Details of specific shortcomings identified in the KUH report (points i to viii) that apply to the transplants performed on the UK patients are as follows:

i. **Insufficient evidence from animal studies to indicate safety.** A recent study using rabbits published by the UCL surgeons suggests that transplantation of ‘tissue-engineered’ tracheal grafts is not safe, as all the transplanted grafts collapsed\(^28\). However, this study was conducted some years after it was tested in two child patients (Patients D and E in the above list), and after approval for the Inspire trial was granted by the UK Medicines and Healthcare products Regulatory Agency (MHRA). Likewise, a pig study recently published by the same group suggests transplantation of ‘tissue-engineered’ laryngeal grafts is neither safe nor effective\(^29\), as the grafts fragmented into small pieces; this was published after MHRA approval was granted for the RegenVox trial.

ii. **No evidence to suggest that seeding a patient’s bone marrow ‘stem’ cells on a tracheal graft is of any benefit.** This point has also been highlighted by an earlier UCL investigation into an allegation of research misconduct\(^30\) relating to the 2012 *Lancet* publication\(^31\) describing the procedure performed on Patient D:

> “These figures [data presented in the publication\(^31\)] had in the Panel’s view not given sufficient emphasis to the presence and possible contribution of the stent and omentum tissue wrap in the recovery of the child patient. Furthermore, the Panel felt that none of the evidence presented by Professor [X] in this published report in fact serve to demonstrate that the addition of stem cells to the transplanted tracheal scaffold used in the patient case concerned played any therapeutic role in the functioning of the trachea and that none of the effects that were demonstrated in these published reports could be directly linked to the beneficial effects of stem cells.” \(^30\)

iii. **Administration of untested growth factors.** Similarly to Andemariam Beyene\(^11\), Patient D, was treated with erythropoietin (EPO), granulocyte colony stimulating factor (G-CSF) and non-clinical grade transforming growth factor beta 3 (TGF-β3), in the absence of any clear scientific rationale, and without first showing safety and efficacy in an animal model\(^31\). The TGF-β3 had not been approved for human use\(^11\).

iv. **Lack of critical expertise.** The KUH investigation highlights that the multidisciplinary panels that approved the transplants at KUH lacked the expertise required to critically appraise the procedures. Did the multidisciplinary panel at the UK MHRA who approved the Inspire and RegenVox trials have the necessary expertise? For instance, did the panel include a head and neck surgeon who was independent from those proposing the trial?

v. **The KUH investigation concluded that the trachea transplant patients should not have been operated on under ‘compassionate use’ because there was no imminent risk of death.** This criticism also applies to one of the transplants performed at Great Ormond Street Hospital (GOSH) (a BBC documentary shows that patient E had a reasonable quality of life before the transplant but died just a few weeks after\(^27\). The KUH investigation\(^11\) concluded that such practice contravenes the Declaration of Helsinki. An opinion piece co-authored by a member of the UCL team explains that a paradigm shift is needed to expedite clinical testing of novel therapies, and suggests that compassionate use cases could be used in place of animal models:
Written evidence submitted by Professor Patricia Murray and Raphael Lévy (RES0022)

“Patients are treated on the basis of clinical need outside of a trial. Clinical outcome and adverse event data are retained and used in place of or in addition to relevant preclinical animal data in subsequent dossiers for submission of the same product in a formal clinical trial. Importantly, these first-in-man compassionate studies are powerful ways to inform robustly designed formal trials, which are often complex and require frequent amendments. These processes will expedite the testing of novel therapies...” 32

This poses a risk to patients because the desire to test an innovative therapy could take priority over doing what is best for the patient, which could well be a more standard or conservative treatment. In their application to MRC to fund the RegenVox trial, the following comment is made by the applicants in regard to Patient E:

“...however and, importantly, her case afforded an opportunity to ‘field-test’ the GMP procedures, protocols and quality control measures included in the present project...” 38

vi. Patients and/or their families were not told of the unfavourable outcomes of previous patients having similar treatment. This appears to have been the case with Patient E in the BBC documentary27 as it seems her family were only told about one previous successful operation (Patient D) and were not informed of the unsuccessful operation performed on Patient C. Indeed, the transcript from the documentary suggests that only one such transplant had been performed by the team previously (on Patient D), despite the fact that one member of the team was involved in the transplant performed on Patient C1,24, who had a very poor outcome. Furthermore, the initial ‘patient information document’ describing the Inspire trial did not indicate that many patients who had received similar tracheal transplants had died33.

vii. The KUH report was highly critical of patients being used for marketing purposes, and mentions that the first patient operated on in Sweden (Andemariam Beyene, patient B in UCL inquiry), was used to promote two universities (UCL and the Karolinska Institute), a hospital (KUH) and an individual surgeon (Paulo Macchiarini). The same criticisms could apply to the reporting of Patient A and Patient D, where photographs of members of the surgical team and the patients appeared in the press34 and on the website of UCL35. This practice can lead to patient outcomes and the intervention itself being described in over-hyped terms. For instance, the report on UCL’s website described the intervention as follows: “[Patient X’s] own stem cells were used to build up the donor windpipe” 35. There was no evidence to support this, as highlighted by a previous UCL investigation into research misconduct30 (see 8ii). An unfortunate consequence of such reporting is that it misinforms the public, and more importantly, prospective patients and/or their families, who may then seek out the surgeons in order to have similar operations performed on themselves and/or their relatives (as was the case for Patient C1,24).

viii. Inaccurate reporting of patient outcomes. The Swedish Central Ethics Review Board have recently published its report on research misconduct relating to scientific articles authored by Macchiarini and co-workers, the conclusion being that a series of six papers should be retracted4. A key problem identified in the report was that the scientific articles contained over-hyped descriptions of patient outcomes, which gave the impression that the health benefits of the synthetic tracheas were much greater than they actually were4. This has also occurred in the case of Patient E, who featured in the BBC documentary27. A scientific article published by the team in 2016 suggests that the transplantation of a ‘tissue-engineered’ tracheal graft extended this patient’s life and that her cause of death, just a few weeks later, was unlikely to be related to the graft36:

“while both unfortunately died [referring to Patients C and E], the causes appeared to be unrelated to the grafts...[ ]. and both would almost certainly have died much earlier if untreated.” 36
This is inaccurate because the BBC documentary shows that before the operation, Patient E had a reasonable quality of life and was attending school, so it is difficult to understand how the authors can claim her life was extended, given that she died just a few weeks later:

“In other words, this is not a situation where we’ve got nothing to lose by going ahead - they’ve got quite a bit to lose and this is going to make for a difficult decision. She’s got a reasonable quality of life, she’s got her good friend, she clearly has a sense of humour and enjoying herself - it makes it harder.” [assessment by respiratory consultant, Colin Wallace]

Inaccurate reporting of the outcomes of this patient also occurred in an article published in 2014, where it was said that the transplant dramatically improved Patient E’s quality of life and that she died of unknown complications:

“Although her immediate latency and quality of life was dramatically improved and she was well enough to go home after 2 weeks, she died of unknown complications 2 weeks after discharge.”

In contrast to these two articles, the UCL inquiry indicates that within 48 hours of discharge, the patient “experienced a respiratory arrest and suffered irreversible brain damage and sadly died”. The UCL report, along with a more recent case study published by the group in 2017 suggest that the death of Patient E was indeed related to her graft, because she “developed ventilatory compromise [was unable to breathe]. During bronchoscopic evaluation, there had been progression of the tracheal graft narrowing.”

ix. Over-hyped reporting by respected funding agencies such as the UK Medical Research Council (MRC). There are incorrect descriptions of the airway transplantations on the MRC website. On page 17 of MRC’s 2014-2019 Strategic Plan, there is a section entitled “Making an impact: World first clinical trial of stem cell-engineered larynx (voice box)”. However, despite the title, there is no scientific evidence to suggest that a larynx can be made from stem cells. Furthermore, the first sentence states “In 2008 MRC-funded researchers at University College London carried out the first transplant of a human trachea (wind pipe) reconstructed using stem cells.” This statement relates to the transplant performed on Patient A. As with the larynx, there is no scientific evidence to suggest that a human trachea can be constructed using stem cells (see 8ii).

In an article published online in 2011 there is more incorrect information:

“That was the first time that a transplant [of] an organ built from stem cells had ever been performed in a person and it seemed to work first time. It was a major breakthrough for science and technology”.

This refers to Patient A’s transplant. There was no evidence that stem cells did anything here and the overall impact of this study has been quite negative, as indicated by comments on Pubpeer.

And from the same page: “Having found themselves in certain environments a stem cell will look around and say ‘This has got the correct feel to it, the right stimuli, shape of a muscle, a piece of cartilage, a piece of bone’ and will therefore differentiate in those ways. So, for example, if it’s an environment with lots of other cartilage cells it’ll become a cartilage cell too”. This runs counter to the view of most stem cell experts.

An MRC representative wrote a piece that was published in the national press (the ‘Telegraph’) on this topic, which also contains incorrect information:

“The news from Barcelona and Bristol of a successful transplant using regenerative medicine is a significant development – not only for the patient herself and those similarly affected, but also
because it serves as a proof of principle. It’s the first time we’ve seen full recovery from clinical surgery involving growth of cells around a scaffold.6

This refers to Patient A’s transplant. It is not clear what is meant by “full recovery”. Moreover, there was no evidence that the patient’s cells grew around the scaffold, and even the authors themselves indicate in their discussion that the addition of cells to the scaffold might not have been necessary5.

9. Forthcoming trials: Inspire and RegenVox

Despite the fact that most of the patients who have been transplanted with ‘tissue-engineered’ tracheas have died1, the UK MHRA has given approval for two formal clinical trials to be conducted. The Inspire trial will recruit four patients and will transplant them with ‘tissue-engineered’ tracheas. Shortly after these patients have been transplanted, a European trial called ‘TETRA’ will recruit an additional 48 patients. Patient recruitment for TETRA is expected to start recruiting patients in July 201838. The RegenVox trial will use similar technology to replace part of the larynx, and will recruit ten patients. It is important to note that as yet, there are no convincing data from animal studies to indicate that these procedures are likely to be safe or effective; at least there are no such data in the public domain. A meeting report from April 2014 by the trial lead at UCL states:

“Presently, the group has been using human cells to seed porcine decellularized scaffolds in preclinical studies. The results have been promising and have provided evidence sufficient to obtain permission for 2 formal clinical trials of partial laryngeal and tracheal replacement...” 25

Yet although these data have already secured MHRA approval and funding from Innovate UK (Inspire trial) and the MRC (RegenVox trial), they have still not been published. The only data from pig studies published by the group have been in 2017, and these showed that the human cells did not integrate, and by six months, the scaffold had fragmented into small pieces29.

i. RevenVox funding proposal to MRC. The application to MRC for the RegenVox trial contained inaccurate information about Patients A and E38. Regarding Patient A, the application indicates: “RegenVox includes the leader of the team which implanted the first stem cell-based airway replacement”38. This statement is inconsistent with the recent UCL inquiry, which states: “The specific role requested of Dr X... was to prepare epithelial cells...to be transferred to Barcelona to enable seeding of a decellularised tracheal graft which had been prepared there. Professor X asserted during the Inquiry interview that he was not involved in either the surgery or the clinical decision-making regarding the appropriateness or otherwise of the clinical approach, which was determined by Dr Macchiarini and the local team of thoracic surgeons in Barcelona”24.

The RegenVox application indicates that at four year follow-up, Patient A was “well with normal lung function and healthy graft”38. But from the UCL inquiry, it is now clear that the graft was not so healthy because the patient “developed a recurrence of her bronchial stenosis which required multiple stents”24. Moreover, the graft has since been removed13.

Regarding Patient E, the application indicates: “A second child underwent a successful implant in 2011, but died of non-graft related causes soon afterwards. Her graft was healthy and vascular at time of death...”38. As indicated in 8v above, and in a recent article published by the group39, it can be seen that the team were aware that the graft had collapsed, an event that would have been directly related to her death as it would have caused airway obstruction leading to respiratory failure:
“we were unable to confirm whether the mechanism for acute obstruction was a primary failure of the graft, severe malacia, or secondary to extraluminal compression”. 39

It is also noted that the outcomes for Patient C, which were very unfavourable1-24, were not mentioned in the application38.

ii. Patient information brochure for Inspire. The Inspire patient information brochure from 5th January 2016 was criticised because it failed to mention the outcomes of previous patients who had received ‘tissue-engineered’ tracheas33. The most recent version, dated 5th October 2016, does now refer to some of the previous patients, but the information provided is not correct:

“In 2008, a lady underwent partial tracheal replacement [Patient A] and is alive and well today. In 2010, a ten years old boy [Patient D] had his entire trachea replaced and is also alive, growing and well today. In 2011, a 15 years old girl [Patient E] also had her whole trachea replaced, but died a month later of unknown causes, although her trachea was working at the time of her discharge from hospital. All three patients were seriously ill at the time they received their transplants and would have probably died without tracheal replacement.” 41

The brochure doesn’t indicate that Patient A has had her left bronchus and lung removed13. Furthermore, the information relating to Patient E is not correct; this patient died just over two weeks after her transplant and it is known that her death was related to her tracheal graft (see 8iii)1-24,39. It is also incorrect to say that all three patients would probably have died without tracheal replacement. Patient A has since had her graft removed and is reportedly still alive24; Patient E had a reasonable quality of life prior to the transplant (see 8viii) but died just over two weeks later. The very poor outcomes experienced by Patient Care not mentioned, nor are the outcomes of patients who received similar treatments by other surgeons. An ‘impact’ statement from the University of Bristol in 2014 indicated that the procedure undertaken on Patient A “has already led to the implantation of bioengineered tracheas in at least 14 other patients” 42. The prospective participants in the Inspire trial should be told of the outcomes of these 14 patients, along with any other patients operated on since.

iii. Patient information brochure for RegenVox. The latest version of the RevenVox patient information brochure is dated 19th July 2016 41. The prospective patients are told: “Stem cells are removed from your bone marrow and grown on the scaffold in the laboratory. These cells will form the cartilage in the wall of the scaffold.” 41 There is no evidence that this happens (see 8ii).

The patients are also given incorrect information regarding previous patients:

“The technology behind this trial has been tested by our team in three patients who were critically ill. One adult patient [Patient A] and two children [Patients D and E] received tissue engineered tracheal implants. In each of these patients, a section of trachea was prepared in a similar way and implanted successfully. One of the children died of an unrelated problem soon after having the implant surgery [Patient E], but for two of these patients this treatment was life-saving. The adult patient is alive with minimal symptoms five years after receiving the implant, and the child is alive and well four years after receiving the implant.” 41

As indicated above in 9ii, this information is misleading.

The outcome for Andemariam Beyene is described as follows: “The adult patient survived for two and a half years after implantation before dying from a chest infection” 41. This is also misleading because it fails to highlight the very serious problems that Andemariam experienced as a direct result of this synthetic tracheal transplant11,16.
10. Recommendations:

- In the interests of patient safety, the Inspire and RegenVox trials should be placed on immediate hold until safety and efficacy have been established in pigs. Furthermore, the preclinical evidence used to support the trials should be assessed by international experts in the field of airway surgery.
- University College Hospital and Great Ormond Street Hospital should commission investigations similar in scope to those commissioned by the Karolinska University Hospital and Landspítali University Hospital to identify any shortcomings in how patients were treated and any medical ethics breaches, including whether it was appropriate to treat these patients under ‘compassionate use’.
- No further transplantations of ‘tissue-engineered’ airways should take place under compassionate use until a thorough investigation of the previous cases has been undertaken.
- Scientific publications reporting on the ‘tissue-engineered’ trachea transplants should be investigated for evidence of scientific misconduct. If misconduct is found, including evidence of over-hyping patient outcomes, and/or over-hyping the role of ‘stem’ cells, retractions should follow.
- The practice of using patients to undertake publicity work in order to promote hospitals, universities and individual surgeons and/or researchers should be immediately banned.
- Funding agencies and institutions should ensure that accurate information is provided to the public. This is particularly important in the area of stem cells and regenerative medicine where there are now increasing numbers of private stem cell clinics selling unproven stem cell therapies direct to the public. Patients are likely to put great trust in the information provided by the MRC, in particular, and if they read that stem cells can make organs and tissues when injected into the body, they are likely to believe this, making it more likely for them to visit these rogue clinics.
- There is an urgent need for a debate around ‘compassionate use’ in the UK to see if more stringent regulation is needed to better safeguard patients.
- The current Science and Technology Committee should reconsider the recommendation made by the previous Committee that placed some emphasis on having ‘a more flexible regulatory environment’ for regenerative medicine. This could put patients at risk because regenerative medicine research is an area that needs very stringent regulation.
- Government should solicit the views of a broad spectrum of experts, including those engaged in basic science, when deciding how best to allocate research funding, especially in the field of stem cells and regenerative medicine.

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11. References


7. Submission of Impact Case Study by UCL to the Research Excellence Framework. ‘The world’s first stem cell based transplants: changing the future of organ replacement’: http://impact.ref.ac.uk/CaseStudies/CaseStudy.aspx?id=36409


11. The Citizens For Responsible Care and Research (CIRCARE) website: ‘Macchiarini Fallet Investigation of the activities of transplantation of synthetic trachea, Karolinska University Hospital’: http://www.circare.org/info/pm/fallet-macch-google-20160903.pdf

12. The Declaration of Helsinki is a set of ethical principles regarding human experimentation developed for the medical community by the World Medical Association (WMA). It is widely regarded as the cornerstone document on human research ethics. The Declaration is available on the WMA website: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/


22. 2016 inquiry in regenerative medicine. Session recorded on Tuesday 19 July 2016. Discussion on patient A starts from 15:57: http://www.parliament.uk/business/committees/committees-a-
Written evidence submitted by Professor Patricia Murray and Raphael Lévy  

23. House of Commons Science and Technology Committee. Fifteenth Report Session 2016-2017 on Regenerative Medicine:  
https://publications.parliament.uk/pa/cm201617/cmselect/cmsctech/275/275.pdf


42. Submission of Impact Case Study by the University of Bristol to the Research Excellence Framework. ‘Health benefits, increased public awareness and changes in national policy result from the successful implantation of the first tissue-engineered trachea, created utilising the patient’s own stem cells: http://impact.ref.ac.uk/casestudies2/refservice.svc/GetCaseStudyPDF/40146

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13. Appendix: excerpt from ‘Megagrant’ by Elena Kokurina, describing Patient A’s transplant

Below is an excerpt from a book that contains a description by Macchiarini of how Patient A’s ‘tissue-engineered’ cadaveric trachea was prepared. The English translation of the underlined text is as follows:

"After that [the decellularization], the carcass was sent to the UK to Bristol and the cells were also transported to Bristol".

"Cells were isolated from the bone marrow of [Patient A] and after that they were seeded on the carcass in Bristol".

"The bioreactor was specially made in Italy and also sent to Bristol. The carcass and the cells were grown in the bioreactor for 4 days. After that they were sent to Barcelona".