Special Inquiry into Regenerative Medicine Research at UCL

29 September 2017
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29 September 2017

Dear Vice Provost,

In January 2017 I was appointed to Chair a Special Inquiry into Regenerative Medicine Research at UCL. The terms of reference were wide ranging to permit a thorough investigation of the involvement of UCL and its personnel in regenerative medicine research but with particular focus on the field of tracheal and large airway tissue engineering. My panel and I have addressed these terms of reference comprehensively as can be seen from the report, which I now present to you.

Yours Sincerely

[Signature]

Professor Stephen J Wigmore
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Chapter 1: Introduction

1.1 Background to the Inquiry

The Special Inquiry into Regenerative Medicine Research at University College London (UCL) was instigated by the Vice-Provost (Research) in June 2016. The purpose of the Special Inquiry was to provide an independent investigation of the involvement of UCL and its personnel in regenerative medicine research with a particular focus on tracheal and large airway tissue engineering and UCL’s relationship with Professor Paolo Macchiarini and the Karolinska Institute. It was determined that the Special Inquiry should be separate from UCL’s procedures for investigating and resolving allegations of misconduct. It was, however, acknowledged that the outcomes of the Inquiry might result in such procedures being instigated.

The Inquiry was formally announced in September 2016.

Professor Stephen Wigmore was appointed to lead the Special Inquiry in January 2017.

The Chair, in consultation with UCL’s Registrar, Vice-Provost (Research) and Vice-Provost (Health) appointed the remainder of the Inquiry Team. The Inquiry Team was supported by a Secretary who was appointed by UCL’s Registrar from UCL’s Student and Registry Services. In turn, the Secretary and Inquiry Team were provided with legal support from a senior Partner from the international law firm, CMS Cameron McKenna Nabarro Olswang LLP.

Previously, in May 2015, UCL’s Director of Research Services had put together a report outlining key issues in the wake of the high profile investigations undertaken by the Karolinska Institute into Professor Paolo Macchiarini (who had held an honorary Professorship at UCL) and the then suspension, and thereafter termination of employment of Professor Alexander Seifalian. In addition, a number of research misconduct allegations relating to:

- research projects involving tracheal replacements constructed from a decellularised organ scaffold;
- tracheal replacements constructed from POSS-PCU; and
- further research projects involving the use of POSS-PCU

had been brought to the Director of Research Services' attention.

UCL has considered four cases under its research misconduct procedure relating to research projects at UCL involving POSS-PCU.

1.2 Terms of Reference

The Inquiry's Terms of Reference are as follows:

a) To provide the Vice-Provost (Research) with an independent report on the full facts of UCL's involvement in regenerative medicine research.

b) To report on UCL's relationship with Professor Macchiarini and the Karolinska Institute in Sweden.
c) To review and comment on the procedures followed for ethics approvals received for UCL’s regenerative medicine research, particularly in cases where there have been trials involving people and animals.

d) To review and comment on the evidence base for the use of POSS-PCU and artificial scaffolds, taking account of data used in trials of this material.

e) To consider any other factors relevant to the Inquiry or requested by the Vice-Provost (Research).

f) To make recommendations to the Vice-Provost (Research) as a result of the findings of the Inquiry.

The Terms of Reference were purposely sufficiently broad in nature to allow the Inquiry Team to explore as many avenues relating to UCL's regenerative medicine research and UCL’s relationships with Professor Macchiarini and the Karolinska Institute as it deemed necessary and appropriate.

1.3 Scope of the Inquiry

Although the Inquiry was initiated by UCL it became clear very early on that the involvement of individuals and clinical cases in for example UCL Hospitals (UCLH), the Royal Free Hospital (RFH) and Great Ormond Street Hospital (GOSH) meant that the scope of the Inquiry needed to include consideration of the activities of UCL Partner organisations. Similarly, the requirement to understand the governance framework relevant to patients involved in compassionate use or clinical trials of Regenerative Medicine products necessitated approaching Medical and Research Directors and other individuals from partner organisations. Many of the individuals involved in research in regenerative medicine hold both academic and NHS contracts and similarly products manufactured within both a University and NHS setting have been used to treat patients. Therefore, in order to address the Terms of Reference in a comprehensive manner, it has been necessary to investigate aspects of both academic and clinical settings.

While one of the Terms of Reference was to report on the full facts of UCL’s involvement with regenerative medicine research it was always the intention that the Inquiry would focus mainly on airway transplantation and the POSS-PCU-related research programmes. No systematic analysis of the many other UCL regenerative medicine programmes has been undertaken. To do so would have required resources, capabilities and time beyond the capacity of the Inquiry. The Inquiry has, however, exercised the freedom to follow the lines of evidence to appropriate conclusions. Similarly, the Inquiry did not revisit decisions made through due process by other authorities or bodies such as multidisciplinary teams, the use of medicine committees, ethics committees, regulatory authorities, academic misconduct review panels and grant awarding committees. Reviewing the work of these duly appointed authorities and bodies was beyond the scope of the Inquiry. The Inquiry did, however consider carefully the clarity of, and compliance with, process and the way in which this governance system is functioning in the context of a complex set of organisational structures.

Finally, the Inquiry is aware that there are ongoing and strongly felt arguments between experts in airway transplantation concerning the optimal strategy for tracheal replacement. The Inquiry team are not experts in airway transplantation and have not taken a position on
these arguments. We are of the view, however, that the best way to resolve issues of genuine uncertainty and professional disagreement is through properly structured nonclinical studies and clinical trials and that organisational systems need to be structured in such a way as to facilitate these processes.

The Inquiry undertook a close examination of the events relating to airway transplantation and the POSS-PCU-related research programmes. We have drawn conclusions on a number of specific and systems-related issues based on the oral testimony and documentary evidence presented. Our recommendations flow from these conclusions.
Chapter 2: How the Inquiry Worked

2.1 Introduction

The intention of this Chapter is to set out some aspects of the work undertaken by the Special Inquiry team:

- in preparation for the oral interviews of witnesses,
- during the oral interviews of witnesses,
- when requesting and receiving written submissions of evidence, and
- in preparing this Report.

2.2 Preparation

The Special Inquiry's Terms of Reference were approved and issued by UCL's Vice-Provost (Research) as part of the commissioning process. Following this, UCL's Registrar sought to appoint a Chair and convene an Inquiry Team. Professor Stephen Wigmore, Professor of Transplantation Surgery at the University of Edinburgh, agreed to Chair the Special Inquiry into Regenerative Medicine Research at UCL and thereafter began to contact potential members of the Inquiry Team. Members of the Inquiry Team were selected on the basis of their expertise in their respective fields, the very high regard in which they are held and for their independence and impartiality. The following individuals were appointed:

- Professor Alicia El-Haj (Professor of Cell Engineering, Keele University),
- Professor David Tosh (Professor of Stem Cell & Regenerative Biology, University of Bath),
- Professor Marc Turner (Professor of Cellular Therapy, University of Edinburgh and Medical Director, Scottish National Blood Transfusion Service), and
- Professor Pankaj Vadgama (Professor and Director of IRC in Biomedical Materials).

The Inquiry Team were issued with formal appointment letters and were required to sign a declaration of impartiality, noting any potential conflicts of interest. To the extent that any potential conflicts were disclosed the Chair considered these carefully. They were all remote and/or minor in nature and the Chair deemed that that they would not have any bearing on impartiality.

To support the Special Inquiry, a Secretary, Mr Edward Payne, was appointed from UCL's Student and Registry Services. Legal support and guidance was provided by Mr Laurence Ward from the international law firm, CMS Cameron McKenna Nabarro Olswang LLP (CMS) who also managed the collection of submissions/documentation gathered for the Inquiry.

The Secretary to the Inquiry Team, CMS, UCL's Legal Services and UCL's Registrar met on several occasions prior to the establishment of the Inquiry Team to discuss the logistics of the Inquiry and the document gathering process, in addition to providing more general advice based on previous similar inquiries.

A webpage (Special Inquiry Webpage) was set-up, which announced in September 2016 that a Special Inquiry had been launched by UCL's Vice-Provost (Research). In time, the webpage
also documented the finalised Terms of Reference and housed a "Call for Evidence", which managed to capture several written responses.

The Call for Evidence was also sent on behalf of the Inquiry Team by UCL's Communications and Marketing manager to field-specific magazines and journals.

2.3 Document Gathering Process

CMS provided a secure extranet site through which Inquiry members could communicate and also share and store documents. Access to the extranet was limited to the Inquiry Team, the Secretary and CMS.

During the document gathering process a significant amount of documentation was sourced and uploaded on to the extranet site. This included:

- publications from journals,
- documentation from previous allegations of research misconduct,
- email correspondence,
- regulatory documentation relating to research grants and funding, and
- initial written responses that the Secretary had received following the announcement of the launch of the Special Inquiry.

The volume of documentation considered by the Inquiry Team was extensive and required expert knowledge to begin piecing together the scope and direction that the Inquiry should take. Based on the documentation that had initially been gathered, the Chair, in collaboration with the Inquiry Team, was able to identify key protagonists who it was felt were important to interview or, if they were unwilling or unable to attend an interview, should be asked to provide a written statement.

2.4 Invitation to Attend an Interview

A formal letter was written and sent by the Secretary on behalf of the Chair, inviting various individuals to attend an interview with the Inquiry Team. Each letter was drafted under the guidance of CMS and provided background information relating to the Inquiry and briefly outlined the reasons for inviting that individual.

CMS’s input into the drafting of these letters was invaluable. As the Special Inquiry was not a Statutory Inquiry under the Inquiries Act 2005 it could not compel the attendance of witnesses and it could not take evidence under oath. In short, the participation of witnesses was voluntary. However, interviews with witnesses could be, and were, conducted in private.

 Witnesses invited for interview were provided with a copy of the Terms of Reference and details of the complete Inquiry Team.

2.5 Written Statements and the Statement Taking Process

Potential witnesses who indicated that they were unwilling or unable to appear in person were encouraged to do so, failing which, they were requested to provide written evidence.

In these circumstances, the Chair drafted a series of questions for the relevant witness to answer. For convenience, all written statements were received by the Secretary to ensure a
In addition, following the Call for Evidence, both the Chair and the Secretary to the Inquiry received written submissions from a number of individuals and organisations providing evidence for the Inquiry Team to review and consider. The submissions were then uploaded onto the extranet site.

2.6 Interviews and Transcription Process

Interviews of witnesses took place across four days: 27 – 28 February 2017 and 24 – 25 April 2017. The first two dates in February primarily involved UCL members of staff and were essentially a background “fact-finding” exercise. These initial interviews helped focus the Inquiry Team's evidence gathering efforts and preparation for the main group of interviews, which took place at the end of April 2017.

The February interviews took place on UCL's Bloomsbury Campus, whilst the April interviews were held in the University of London Garden Halls. The Secretary actively sought a suitable venue for each set of interviews to take place. Given that the first set of dates were to meet with UCL members of staff only it was deemed appropriate to hold the interviews on UCL's main campus as a central point for witnesses to attend. As regards the April interviews the Secretary felt that given there were considerably more external witnesses, the University of London Garden Halls, Cartwright Gardens would make for a more favourable and central location.

The witness interviews held in April were recorded by a professional transcription company to ensure that the Inquiry obtained a detailed and accurate record of the evidence provided. The transcript of each interview was subsequently sent to the applicable witness. The Chair was acutely aware that acronyms and medical terms would be prevalent throughout, which might have caused difficulties. Accordingly, a glossary of terms, likely to be referred to during the course of interviews, was produced for the transcribers in advance.

The room was set up prior to the commencement of the April interviews with microphones in front of each person to ensure the effective capturing of the interview. Two transcribers were working at any given time, in real time, which enabled a full copy of the transcript to be sent to the Secretary at the end of each day.

The Inquiry Team decided that it was not necessary for the February interviews to be transcribed. Instead, the Secretary and Mr Ward from CMS took notes, which were typed up, agreed upon and uploaded onto the Inquiry Team's extranet site.

During the course of the interviews it became apparent that there were at that time several gaps in the evidence gathered. Accordingly, several additional witnesses were invited at short notice to take part, all of whom were readily available and agreed to do so.

Following the interview stage a further period of documentation gathering took place to ensure that, insofar as possible, all of the facts were supported by written evidence. In addition, the Chair also decided that it would be helpful if written statements could be provided from other witnesses who, up until that point, had not been involved.

Following receipt of the draft transcripts from the April interviews, the Chair, the Secretary, and CMS reviewed them to check for points of accuracy, errors and omissions (on occasion the transcribers and recordings had failed to pick up precisely what a witness had spoken
This was a painstaking task reviewing interviews, which varied in length from 30 minutes up to 90 minutes in some cases. The interview transcripts were then sent to respective witnesses by the Secretary to review and (where necessary) to clarify any outstanding points of accuracy or inaudible transcription. Thereafter, having regard to any comments received, they were finalised and they represent an accurate record of each interview.

2.7 Production of the Report

A further meeting took place at the start of May 2017 with the Inquiry Team, the Secretary and CMS to determine the structure and content of this report. It was agreed that the report would address each of the Terms of Reference, in addition to providing UCL with a series of recommendations in light of the findings of the Inquiry Team. The objective was to complete the Report by the end of June 2017.

During the writing of the report, however, the critical evaluation and cross-referencing of evidence revealed a number of areas where there was lack of clarity or discrepancies between the evidence provided by different witnesses. In addition there was specific concern that evidence that emerged quite late in the process in respect of the manufacture of POSS PCU constructs for clinical application may have wider implications. A further series of letters of clarification were sent by the Chair and UCL was informed of the issue of concern. It was therefore decided to allow a further 2 weeks for responses and some further time thereafter to consider the additional evidence and to finalise the Report.
Chapter 3: UCL and Regenerative Medicine Research

3.1 Introduction

Founded in 1826, UCL was the first university institution in London. In 1836 UCL became one of the two founding colleges (along with King's College London) of the University of London. UCL grew through mergers with other institutions to become the largest constituent member of the federated University of London. In 1976 a new Royal Charter restored it's legal independence and in 1993 it gained degree awarding authority independent from the University of London. It has around 38,000 undergraduate and postgraduate students and more than 11,000 staff. As a research organisation, UCL has an income of £1.36 billion.

3.2 Partner Organisations

University College London Hospitals NHS Foundation Trust or UCLH comprises the following hospitals:

- University College Hospital (incorporating Elizabeth Garrett Anderson Wing (maternity), University College Hospital Macmillan Cancer Centre, the Institute of Sport, Exercise and Health, Hospital for Tropical Diseases and Westmoreland Street);
- Royal National Throat, Nose and Ear Hospital;
- Royal London Hospital for Integrated Medicine;
- National Hospital for Neurology and Neurosurgery; and
- Eastman Dental Hospital

UCLPartners Academic Health Science Partnership or UCLPartners is an academic health science partnership first created in 2009 with aim of translating cutting-edge research and innovation into measurable health and wealth gain for patients and populations – in London, across the UK and globally. Programmes of work are responsive to the needs and experiences of patients receiving care in its local population of six million people in northeast and north central London, south and west Hertfordshire, south Bedfordshire and southwest and mid Essex. Its partner organisations comprise 23 NHS Trusts (including UCLH), 10 Higher Education Institutions (including UCL), 20 Clinical Commissioning Groups and 3 other affiliated organisations. The full list of all partner organisations can be found here: https://uclpartners.com/who-we-are/our-roles/academic-health-science-centre-ahsc/.

UCL Business or UCLB is a public limited company whose mission is to commercialise research from UCL and NHS Trusts associated with UCL including UCLH, GOSH, the Royal Free Hospital and Moorfields Eye Hospital.

The Inquiry noted that this is a very large, diverse and complex organisational cluster, which poses challenges in respect of leadership, management and governance.

3.3 Regenerative Medicine

UCL has undergone a number of restructuring cycles. Currently the School of Life and Medical Sciences includes more than 1000 principal investigators and has an annual turnover of around £630 million.
Regenerative Medicine within UCL has more than 100 principal investigators and sits broadly across the Biomedical Sciences in a number of different institutions. UCL’s description of Regenerative Medicine does not, however, include researchers who undertake research in the development of small molecules for pharmaceutical administration, biomaterials without a cellular component or allied fields such as ethics, law or business.

The Inquiry noted that this scope might be a weakness in governance of products, which are not Cell Therapies but are nevertheless intended for direct human clinical application.

3.4 Interaction between Academic and NHS organisations

Many individuals working in clinical medicine and related fields are employed by UCLH or another NHS Trust and, at the same time, hold an honorary contract with UCL. Others are employed by UCL and hold an honorary contract with UCLH or another NHS Trust. These types of contractual arrangement are very common among clinical academics in the United Kingdom and they offer significant benefits in facilitating the development of medical science. However, one of the complexities of this type of contractual arrangement is that it can be unclear at times whether an individual is working for either the University or the applicable NHS Trust. Similarly, with novel or experimental treatments, the boundaries between what should be classified as academic activity and what should be classified as health service related activity might become blurred. Coupled with this, there can be uncertainty or ambiguity around which organisation’s governance framework applies when activities span both (or indeed multiple) institutions.

The Inquiry noted that this is particularly challenging in the field of Regenerative Medicine where frequently products are manufactured in an academic or clinical organisation. This is a qualitative differential from standard pharmaceuticals or small molecules which are normally manufactured by commercial organisations.

3.5 The Organisation of Regenerative Medicine and Cell Therapy within UCL

In 2008/09 attempts were made by UCL to bring together researchers with common interests in the field through the creation of 'The Centre for Stem Cells and Regenerative Medicine'. This grouping was a virtual centre including groups in different buildings and component organisations of UCL. The first Director was Professor Claudio Stern. UCL provided a research administrator, Dr Mariana Resnicoff, whose role was to connect with the people that specialised in this area of research across the organisation(s) and coordinate the activities of the Centre. The Centre had an open door policy and a voluntary membership. The principal purpose was to bring groups and individuals together in a collaborative way to support the development of research. A number of interest groups were created none of which had a formal chair. The attempt was to encourage researchers from different disciplines to cross-fertilise ideas and generate projects through informal discussions. The Centre ran a series of seminars including two large seminars. The first of these was held jointly with researchers from Bangalore and the second focused on Regenerative Medicine and Nanotechnology. The Centre never had a line management or governance role and therefore functioned more as a professional network. There was a feeling among some members of the Centre that UCL was not particularly active in supporting the Centre or its activities. There was a further reorganisation within UCL in 2012. This was attributed to a period of austerity during the recent financial crisis and
money was described as "being tight". Many facilitators and administrative posts including Dr Mariana Resnicoff's were withdrawn as a consequence.

A 'Therapeutic Innovation Network' known as the UCL-wide 'Cell, Gene and Regenerative Medicine Network' later replaced the 'Centre'. This network is currently co-chaired by Professor Emma Morris and Professor Adrian Thrasher. Again, the purpose of this network is to promote academic collaboration and development of cell therapy, gene therapy, tissue engineering and regenerative medicine projects between researchers with similar interests but often working in different locations across UCL. As with the Centre for Stem Cells and Regenerative Medicine, this network does not have a management or governance function for these therapies. An administrator has been provided to support the network.

The extent to which the network formally engages with and is supported by the other organisations within UCLPartners was not clear to the Inquiry. The Cell, Gene and Regenerative Medicine Network also has interactions with UCLB.

3.6 Complexity of Structure

During interviews with senior academics and researchers at UCL a number of themes emerged:

- Researchers are localised within a large number of different organisations, sites and buildings. While this may offer certain advantages, it was also considered to create a degree of fragmentation of research themes and make research collaboration, management and governance difficult.

- Researchers are on occasion isolated, for example in clinical settings when they have basic science interests. The opportunity for academic scientists to work with clinicians offers significant advantages in breaking down traditional organisational and professional barriers and in stimulating multidisciplinary collaboration, but can also pose risks where a researcher becomes isolated from his or her peer group or might be subject to requests or pressures which they are not necessarily equipped to fully understand or assess.

- The fragmented nature of research groups can, on occasion, create confusion over accountability and line management particularly in clinically related activities.

3.7 Current Research Portfolio in Regenerative Medicine

There are a wide range of research programmes within the Regenerative Medicine field being conducted at UCL. The following summaries provided by UCL illustrate the range of activities. Bold text indicates that clinical trials are already in progress or are in the process of being set up.
### Cells for repair/ regeneration

**Acute medicine**
- Angiogenic cell therapy: ischaemic limb

**Cardiology**
- BM SCs, cardiac cells: cardiac repair
- BM-derived MN cells: acute myocardial infarction
- Magnetic cell targeting: liver fibrosis & coronary artery regeneration (magnetic stent)
- Exosomes: cardiac protection

**Foetal medicine**
- Amniotic fluid SCs: neonatal NEC, pre-term brittle bone disease, neurorepair & protection

**Hepatology**
- Organoids: liver

**GI**
- Enteric nervous system SCs: gut disease
- Pancreatic islet transplantation

**Musculoskeletal**
- MSCs (BM, adipose) – tendon (ASCAT), cartilage, bone & muscle repair
- Skeletal muscle stem cells: muscular dystrophies
- Pluripotent mesodermal medicine (EU)

**Neurology**
- Cortical implant for optogenetic neural control (CANDO collaboration): epilepsy
- Olfactory ensheathing cells (autologous & allogeneic) – GMP production for nerve repair
- ES-derived motor neurones – ALS
- Neural transplantation (Allogeneic) for PD (Transneuro, Cambridge)
- Neural tissue – peripheral nerve repair (EDI)
- Enteric nervous system SCs: spinal cord repair

**Ophthalmology**
- ESC & hiPSC-derived retinal pigmented epithelial (RPE) cells including optogenetically controlled – macular degeneration (SMD® & wet & dry AMD®)
- ESC & hiPSC-derived photoreceptor cells (PR)
- Endothelial progenitors: diabetic retinopathy
- Musculoskeletal: conjunctival epithelial-derived cells, corneal stromal SCs with RAFT collagen matrix technology, corneal transplant: corneal repair
- Muller stem cells: retinal dystrophy
- Novel delivery mechanisms

**Renal**
- Kidney SCs, amniotic fluid SCs: renal disorders
- Pancreatic islet transplantation

**Tissue engineering**

**Cardiology**
- Regenerative heart valve: ESPOIR (EU)
- Calcification-resistant porcine pericardial heart valve safety (Translink, EU)

**ENT**
- Ear

**Craniofacial**
- Adipose-derived SCs: facial bone

**GI**
- Intestine; oesophagus

**Hepatology**
- Liver

**Immunology**
- Thymus

**Musculoskeletal**
- MSCs (multiple sources): tendon, bone, cartilage, tendon-bone attachment

**Ophthalmology**
- Corneal stem/epithelial cells: RAFT technology

**Renal**
- Pancreas

**Respiratory**
- BM-derived MSCs & epithelial cells: larynx - RegenVox; trachea - Inspire, Reline; lung

**Urinary**
- Bladder

**Scaffold development/ optimisation**
- Osseochondral scaffolds, respiratory scaffolds (angiogenesis), electrospun facial scaffold

**3D printing**
- Trachea, polymeric scaffolds

**3D tissue models**

**Biomimetic techniques**

*Bold indicates clinical trial open or in set-up*
3.8 Clinical Trials

A number of clinical trials involving Advanced Therapy Medicinal Products (ATMPs) are being planned or undertaken at UCL or within UCLPartners (UCLP). The definition of ATMPs is found in Eudralex Directive (2001/83/EC) as amended by the ATMP Regulation 1394 / 2007 and lays out 4 categories as follows:


- Somatic cell therapy medicinal products (as defined in Part IV of Annex 1 of Directive 2001/83/EC Eudralex, the Rules Governing Medicinal Products in the European Union)

- Tissue engineered products (as defined in Article 2(1)(b) of the Advanced Therapy Medicinal Product Regulation (EC) No. 1394/2007)

- Combined advanced therapy medicinal products are defined in Article 2(1)(d) of the Advanced Therapy Medicinal Product Regulation (EC) No. 1394/2007. In summary, they are ATMPs that incorporate one or more medical devices or one or more implantable medical devices and they also meet certain other specified conditions.

These terms are explained in the Glossary.

The following tables summarise the ATMP clinical trials which are being planned or undertaken involving UCLP currently:
<table>
<thead>
<tr>
<th>Managing organisation</th>
<th>ITREC</th>
<th>TACTICAL</th>
<th>ALLCAR19</th>
<th>CARD</th>
<th>COBALT</th>
<th>CARPALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td>Immunotherapy with Tacrolimus resistant EBV CTL for lymphoproliferative Disease after Solid Organ Transplant</td>
<td>Targeted stem cells expressing TRAIL as a therapy for lung cancer</td>
<td>Immunotherapy for high risk ALL using CAR T-cells to target CD19 as a bridge to allogeneic transplantation</td>
<td>CAR19 Donor Lymphocytes for relapsed CD19+ malignancies following allogeneic transplantation</td>
<td>Evaluation of CAR19 T-cells as an optimal bridge to allogeneic transplantation</td>
<td>Immunotherapy with CD19 redirected T-cells for high risk/relapsed paediatric CD19+ ALL and other haematological malignancies</td>
</tr>
<tr>
<td>Status</td>
<td>In set-up - to open Q2 2018</td>
<td>In set-up - Regulatory submission Q4 2017</td>
<td>To open around August 2017</td>
<td>Recruiting</td>
<td>Recruiting</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Funder</td>
<td>MRC</td>
<td>NIHR INV</td>
<td>EU FP7 - ATECT</td>
<td>ICR</td>
<td>GOHS, Mouton, CWL</td>
<td></td>
</tr>
<tr>
<td>CI</td>
<td>P. Amrolla</td>
<td>S. James</td>
<td>K. Peggs</td>
<td>E. Peggs</td>
<td>E. Peggs</td>
<td>P. Amrolla</td>
</tr>
<tr>
<td>Design</td>
<td>Phase I, multicentre, single arm</td>
<td>Phase II: dose titration, single arm</td>
<td>Single site, dose-escalation (3 cohorts), Phase I</td>
<td>Single site, dose-escalation (3 doses per pt), Phase I</td>
<td>Phase I, single arm dose escalation (3 cohorts)</td>
<td>Single arm, multicentre, non-randomised, Phase I</td>
</tr>
<tr>
<td>Aim</td>
<td>Determine the safety of tacrolimus resistant autologous EBV CTL and compare expansion/persistence with control EBV CTL in solid organ transplant patients with PTLD</td>
<td>Evaluating safety &amp; anti-tumour activity of MSCAIR &amp; chemo in metastatic NSCLC</td>
<td>Evaluating feasibility of bridge to Transplant, feasibility of generating CAR, safety of administering CAR</td>
<td>Evaluating feasibility of bridge to transplant, feasibility of generating CAR, safety of administering CAR</td>
<td>Evaluating feasibility of bridge to transplant, feasibility of generating CAR, safety of administering CAR</td>
<td>Evaluating safety, efficacy &amp; duration of response</td>
</tr>
<tr>
<td>Disease</td>
<td>Post-transplant lymphoproliferative disease (PTLD)</td>
<td>Non Small Cell Lung Cancer (NSCLC)</td>
<td>CD19+ high risk/relapsed B-ALL</td>
<td>CD19+ malignancy relapsed post allo-transplant</td>
<td>CD19+ DLBCL</td>
<td>CD19+ high risk/relapsed haematological malignancy</td>
</tr>
<tr>
<td>ATIMP</td>
<td>3) Autologous EBV-CTL transduced with the genetic retroviral vector for CNA8 transduction resistant to tacrolimus 2) Autologous EBV-CTL transduced with the control retroviral vector for CNA8</td>
<td>MSCAIR</td>
<td>Autologous CD19CAT-41882 CAR T-cells</td>
<td>Allelicergic RBB/467 CAR T-cells (or autologous)</td>
<td>Autologous RBB/467 CAR T-cells</td>
<td>Autologous CD19CAT-41882 CAR T-cells</td>
</tr>
<tr>
<td>Age</td>
<td>1-70 years</td>
<td>2-18 years</td>
<td>16-65 years</td>
<td>16-70 years</td>
<td>16-65 years</td>
<td>&lt;24 years</td>
</tr>
<tr>
<td>Nt Patients</td>
<td>10 patients treated (18 enrolled)</td>
<td>Phase I: min 6 and Phase II: 40</td>
<td>approx 20</td>
<td>12 treated</td>
<td>12 treated (*3 / cohort)</td>
<td>15 treated (18 recruited)</td>
</tr>
<tr>
<td>Sites</td>
<td>GOSH, KCL, 7 RFH, ? UCLH</td>
<td>UCLH, Christie Manchester, 7 RFH</td>
<td>UCLH</td>
<td>UCLH</td>
<td>UCLH</td>
<td>GOSH, UCLH, Manchester Children's Hospital</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Toxicity within 6 weeks of infusion &amp; persistence/frequency of EBV-CTL in PB</td>
<td>Toxicity, feasibility of generating CAR</td>
<td>Toxicity, feasibility of manufacturing, toxicity</td>
<td>Toxicity, complete tumour response, feasibility of adequate leukaemia collection and generation of CAR</td>
<td>Toxicity, proportion of patients achieving molecular remission at 1 month post CAR</td>
<td>Toxicity, proportion of patients achieving molecular remission without further therapy at year 2, persistence &amp; frequency of CAR cells in PB, incidence and duration of hypogammaglobulinaemia ia, relapse rate/DFS &amp; OS at 1 and 2 years</td>
</tr>
<tr>
<td>Secondary endpoint</td>
<td>Disease response at 1/2yrs, relapse rate at 1/2yrs, organ graft rejection at 1/2yrs</td>
<td>Proportion &amp; depth of achieved responses at 18 months post IMP, Persistence and frequency of CAR assessed by flow and qPCR, incidence/duration hypogammaglobulinaemia ia, relapse rate, DFS, OS at 1/2 yrs</td>
<td>Engraftment, expansion &amp; persistence, depletion of b-cell compartment, timing &amp; magnitude of CRS</td>
<td>Engraftment/expansion &amp; persistence of CAR, depletion of b-cell compartment, timing &amp; magnitude of CRS, PET-CT response @ 28 days, Np patients proceeding to allo-transplant</td>
<td>Proportion in molecular remission without further therapy at year 2, persistence &amp; frequency of CAR cells in PB, incidence and duration of hypogammaglobulinaemia ia, relapse rate/DFS &amp; OS at 1 and 2 years</td>
<td></td>
</tr>
<tr>
<td>ICAT</td>
<td>COSTPALL</td>
<td>GOE</td>
<td>FIX</td>
<td>CMV</td>
<td>ASCAT</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td><strong>Managing organisation</strong></td>
<td>CTC</td>
<td>CTC</td>
<td>JRO</td>
<td>JRO</td>
<td>JRO</td>
<td></td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Recruiting</td>
<td>Recruitment closed - in long-term P0</td>
<td>In set-up</td>
<td>In set-up</td>
<td>Open</td>
<td>Open / recruiting</td>
</tr>
<tr>
<td><strong>Funder</strong></td>
<td>MRC</td>
<td>EU FP6</td>
<td>MRC and Biomin</td>
<td>Freeline Therapeutics Limited</td>
<td>MRC</td>
<td>Stem Cell Foundation</td>
</tr>
<tr>
<td><strong>CI</strong></td>
<td>P. Amore</td>
<td>P. Amore</td>
<td>Pratima Chowdary</td>
<td>Pratima Chowdary</td>
<td>Emma Morris</td>
<td>Andrew Goldberg</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Multi-centre, randomised Phase II trial</td>
<td>International, randomised Phase II</td>
<td>International, Multi-site, single arm, Phase II, dose escalation</td>
<td>International, Multi-site, single arm, Phase II, dose escalation</td>
<td>Multi-site, Phase II, dose escalation</td>
<td>Phase II, proof of concept pilot study, open label, single arm, single centre</td>
</tr>
<tr>
<td><strong>Aim</strong></td>
<td>Determining whether adoptive immunotherapy with allogeneated donor T-cells can be safely used to improve T-cell reconstitution post unrelated donor SCT</td>
<td>Evaluating the feasibility, safety, biological effect of adoptive transfer of CD35/Recombinant chimera receptor transduced EBV CTL in relapsed 9-cell precursor ALL post SCT</td>
<td>To assess the safety of systemic administration of our novel single-stranded AAV2/HLP- FVIII-V3 vector in adults with severe haemophilia A over three dose levels 6x10^11, 2x10^12, and 6x10^12 vg/kg</td>
<td>To assess the safety of systemic administration of AAV5-S3-HPL2-Ti-FX in adults with haemophilia B at up to three different dose levels.</td>
<td>To test the feasibility of generating donor-derived CMV specific T cells and to test the safety, toxicity and efficacy of CMV TCR-transduced T cells used for the pre-emptive treatment of CMV reactivation following HLA matched sibling AHSCT.</td>
<td>To evaluate safety and efficacy of autologous bone marrow derived culture expanded MSCs injected into the tendon and to gain experience in using Ultrasound Tissue Characterisation (UTC) and assess usefulness of UTC as an outcome measure.</td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td>Haemostatic malignancies</td>
<td>CD35-9-cell precursor ALL or relapsed ALL</td>
<td>Haemophilia A</td>
<td>Haemophilia B</td>
<td>Recipients of Allogeneic Haematopoietic Stem Cell Transplantation.</td>
<td>Achilles Tendinopathy</td>
</tr>
<tr>
<td><strong>ATIMP</strong></td>
<td>CD3/71 allogeneated donor cells</td>
<td>Donor derived EBV specific CTL / Irradiated donor- derived lymphoblastic cell line (LLL)</td>
<td>Adeno-associated viral vector encoding FVIII-V3</td>
<td>AAV-S3-HPL2-Ti-FX</td>
<td>Adeno- associated viral vector encoding FX</td>
<td>CMV TCR transduced donor-derived T cells</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>≥ 16 years</td>
<td>≥ 18 years</td>
<td>≥ 18 years</td>
<td>18-65</td>
<td>18-70</td>
<td>18-10</td>
</tr>
<tr>
<td><strong>No Patients</strong></td>
<td>24 (16 active / 8 controls)</td>
<td>17/10 (12 pre-emptive, 5 prophylactic)</td>
<td>Up to 18</td>
<td>Upto 18</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td><strong>Sites</strong></td>
<td>University of Manchester, Manchester; BHF (Leeds), Leeds; Münster, Essen, Hannover, (Frankfurt)</td>
<td>Z/UL, approx 0 US</td>
<td>11 EU sites (France, UK, Germany, Italy, Sweden, Netherlands) and 5 sites in US</td>
<td>4 UTC sites (Birmingham, USA, Nottingham, Bristol, UCLA)</td>
<td>1 site (CNMHC)</td>
<td>1 site (INRUK)</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Circulating CD3 count at 4 months post SCT</td>
<td>Toxicity at 12 weeks and biological efficacy (VMA in BM at 12 weeks)</td>
<td>(1) Dose limiting toxicity including any Grade III or greater adverse events (AEs) that are all related to the ATIMP, according to CTCAE v4.03. (2) Neutrophil and platelet count.</td>
<td>(i) Transduction efficiency and TCR expression on TCR-transduced T cells; (ii) Organ specificity and other side effects.</td>
<td>Incidence rate of serious adverse reactions.</td>
<td>Incidence of side effects at 6 months, where success is defined as a reduction of 2 or more points on VAS of pain, an increase of sporting activity score, and an increase of VAS A score greater than the NCO. Conventional ultrasonographic changes from baseline, UTC changes from baseline and correlation between findings of UTC and conventional US.</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td>Incidence of II-V acute and chronic GVHD; time to recovery normal T cells and CD4 counts &amp; normal TCR diversity; in vitro anti-viral response of circulating PBMCs; transplant related mortality &amp; DFS at 1 year post infusion</td>
<td>Persistence and frequency of circulating CTL in PB, in vitro anti-leukemic response of circulating PBMC (elispot) and release rate, DFS, OS at 1 and 2 years</td>
<td>The proportion of patients achieving hVIII activity at or above 15% of normal at week 12; The proportion of patients achieving hVIII activity at or above 40% of normal at week 12; haemostatic effectiveness; immune response; viral shedding</td>
<td>Endogenous hFX Production; haematostatic effectiveness; immune responses; viral shedding.</td>
<td>CMV specific immune responses at TCR transduced T cells pre- and post-infection using in vitro functional assays, such as intracellular cytokine secretion; (ii) CMV responses post-infection of CMV TCR-transduced T cells; (iii) Incidence and severity of GVHD post infection of CMV TCR-transduced T cells; (iv) immune reconstitution; (v) Persistence of TCR-transduced T cells.</td>
<td>Incidence of success at 6 months, where success is defined as a reduction of 2 or more points on VAS of pain, an increase of sporting activity score, and an increase of VAS A score greater than the NCO. Conventional ultrasonographic changes from baseline, UTC changes from baseline and correlation between findings of UTC and conventional US.</td>
</tr>
</tbody>
</table>
The Inquiry is aware of other research projects and clinical trials not listed above, pointing to the difficulty the organisation has in keeping visibility of all the relevant activity being undertaken across the organisational cluster.

### 3.9 Conclusions

UCLP is a large, complex multi-disciplinary set of organisations operating from multiple geographically dispersed sites. This type of organisational structure poses particular challenges in respect of leadership, management and governance, particularly in the context
of Regenerative Medicine where medicinal products are frequently manufactured in the academic or clinical environment and the boundaries between academic research, manufacturing, and clinical treatment may become blurred. It may become unclear which organisational partner is responsible for governance of which part of the value chain. This challenge extends to products such as medical devices and small molecules that are not Cell Therapies but may nevertheless be intended for human clinical application. Moreover, where there are different governance structures within different organisations, different nomenclature in use, and different levels of understanding of the quality and regulatory requirements between different partners, then communication and end to end oversight might be compromised. The Inquiry considered that this is a problem of ‘meta-governance’ of the organisational cluster and that the evidence suggests that there is no single part of the structure that has full systematic governance visibility over the whole of the Regenerative Medicine field – the Cell, Gene and Regenerative Medicine Network not having been structured, scoped or resourced for this purpose. The Inquiry therefore went on to examine whether there was evidence of structural governance weakness.
Chapter 4: Manufacturing, Clinical and Research Governance

4.1 Manufacturing

4.1.1 Manufacture of ATMPs

ATMPs are required to be manufactured at Good Manufacturing Practice (GMP) under Eudralex, the Rules Governing Medicinal Products in the European Union, Volume 4 EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use (Directive 2001/83/EC) and the Advanced Therapy Medicinal Product Regulation (EC) 1394/2007. In the UK ATMP manufacturing facilities are licensed by the Medicines and Healthcare products Regulatory Agency (MHRA).

The Centre for Cell, Gene and Tissue Therapy at the Royal Free London NHS Foundation Trust holds a Manufacturer's Authorisation for Investigational Medicinal Products (MIA (IMP)) which permits the manufacture of these products for clinical trials and a Manufacturing Specials (MS) licence which permits the manufacture of unlicensed medicines to meet the special clinical needs of individual patients.

The Inquiry is of the view that the Centre for Cell, Gene and Tissue Therapy holds all relevant authorisations under the relevant legislation for Cell and Tissue processing and ATMP manufacture.

4.1.2 Manufacture of Medical Devices

The manufacture of Medical Devices is governed by the Active Implantable Medical Devices Directive (90/385/EEC) and the General Medical Device Directive (93/42/EEC) transposed into UK law under the Medical Devices Regulations 2002. Medical Devices should be manufactured using Good Manufacturing Practice (GMP) grade reagents suitable for human use, using validated standard operating procedures within a GMP Quality Management System. The MHRA is the designated Competent Authority in the UK with responsibility for ensuring the compliance of manufacturers and the quality and safety of medical devices, usually thought certification by a notified body. The MHRA released Guidance on the exceptional use of non-CE marked medical devices in December 2004 (https://www.gov.uk/guidance/exceptional-use-of-non-ce-marked-medical-devices) which specifies how a manufacturer can apply for approval to supply non-compliant medical devices (including custom made devices) on humanitarian grounds provided:

- the clinician responsible for the patient's treatment supports the manufacturer's application
- there is no alternative CE marked device available for the treatment
- it can be demonstrated that mortality or morbidity is significantly reduced if the device is used compared to alternative compliant treatment

The manufacturer has the responsibility to apply to supply a non-compliant medical device. However, the manufacturer and the clinician must both complete the required forms listed on the application and submit them to MHRA. Separate applications are required for different patients on a case-by-case basis. The MHRA will usually send the decision to the manufacturer and clinician within 48 hours. Manufacturers also have a responsibility to report adverse incidents to the MHRA.
The Inquiry found no evidence that Professor Seifalian’s research laboratory, used for the manufacture of the POSS-PCU constructs, met the requirements of the Medical Devices Regulations 2002. The 2002 Regulations still apply where the final product is a Combined ATMP.

4.2 Clinical Governance

4.2.1 Clinical Trials Authorisation

Clinical trials of investigational medicinal products must be carried out at Good Clinical Practice (GCP) under the terms of the Clinical Trials Directive (2001/20/EC), and require approval from both an independent ethics committee (under the aegis of the Health Research Authority in England) and a Clinical Trials Authorisation from the national competent authority (the MHRA in the UK). An Investigational Medicinal Product Dossier (IMPD) must be submitted to the MHRA which includes information relating to the quality, manufacture and control of the investigational medicinal product, data from non-clinical studies and from any clinical use (such as on a compassionate basis). A critical analysis of the nonclinical and clinical data in relation to the risks and benefits of the proposed study have to be part of the IMPD.

The clinical governance structure for clinical trials involving human interventions at UCL/UCLH requires review that the appropriate ethics and regulatory approvals supporting the trial have been obtained. This is primarily coordinated through the Joint Research Office with oversight provided by the Clinical Research Governance Committee. A schematic of this pathway is shown below.

The Inquiry concluded that the Clinical Trial Authorisation process in UCLPartners is compliant with the relevant legislation.

4.2.2 Patients undergoing interventions outside of clinical trials

Children

A number of patients receiving cell therapy, gene therapy or tissue engineered procedures do so outside of clinical trials. Great Ormond Street Hospital is an internationally recognised centre for child health and a special NHS Foundation Trust in its own right. GOSH often treats children with exceptionally rare conditions including gene defects, congenital
abnormalities and rare acquired diseases. Such patients often require treatment outside of a clinical trial and their cases are considered by one or more multidisciplinary team meetings prior to presentation of the case to a hospital ethics committee called the Clinical Ethics Service (CES). The basic tenet of the CES is that they do not decide or give approval for any procedure - they help teams and families make decisions in difficult circumstances - the parents and occasionally the child are invited to their reviews and ultimately given informed consent to a treatment offered by a medical team. The composition of the CES has a broad representation with eleven members listed on the GOSH website representing spiritual care, neurology, adolescent medicine and clinical ethics, general practice, general paediatrics, paediatric anaesthesia, a non-executive director of the NHS Trust, a patient advice and liaison manager, critical care and two lay members. The committee is co-chaired by a critical care medicine specialist and a lay member. Communication from the Chair (June 2017) indicates that the committee has been expanded to include 20 members but most meetings will include 12-15 members. In an emergency a "Rapid Review" may be performed but such a meeting still requires the committee to be quorate. The minimum constituency for the committee to be quorate is one bioethicist, one senior clinician and one lay member however, in practice, the committee is always significantly larger than this. Written submission is mandated and most cases then lead to presentation of the case and discussion. The CES meetings are audited and reported to the hospital Clinical Governance Team Annually. Minutes of the meetings are also sent to senior members of the institution management team (Medical Director and or Chief Executive Officer). If the likely alternative to treatment is death then cases have mandated referral to a palliative care specialist who may be co-opted on to the committee to give opinion. One of the criteria of the CES is that the outcome must be reported whether the intervention is effective or not.

**Adults**

Within UCLH, an informal grouping (termed locally the 'three wise men') considers compassionate use or exceptional individual treatment requests for adult treatment. In practice these are experienced male or female clinicians and usually includes the Director of Clinical Safety or the Director of the Joint Research Office and senior clinicians with experience in the subject area of the proposed treatment. The 'three wise men' is not a formal committee and its deliberations are not minuted. Decisions are made on an *ad hoc* basis and are usually recorded in the patient’s medical notes. The UCLH Use of Medicines Committee also has to approve the addition of a novel medicinal product to the formulary. The Use of Medicines Committee is responsible for overseeing all aspects of medicines policy and management and has a multidisciplinary membership drawn from across the Trust. Wherever possible clinicians are encouraged to put patients requiring novel or exceptional use treatments into clinical trials.

The Inquiry noted that the arrangements for oversight and approval of novel medicinal products on a compassionate use basis are appropriate but do vary between different organisations and may not cross-reference a similar product being used in different patients across different organisations within the UCLH cluster.
4.3 Academic Misconduct Investigations

4.3.1 Procedure

UCL has an academic research misconduct investigation procedure that is closely aligned to the model adopted by the UK Research Integrity Office. It is called the "Procedure for investigating and resolving allegations of misconduct in academic research". The procedure has recently been refreshed (effective 1 January 2017) although the basic structure and approach has not changed significantly. The intention of the procedure is to provide a protocol for academic research misconduct screening and investigation, which is fair to all parties.

The UCL Registrar, currently Wendy Appleby is the 'named person' who has responsibility for ensuring the integrity of proceedings conducted under the procedure. The procedure itself has been approved by UCL's Research Governance Committee.

The procedure allows research to be investigated once allegations are made formally in writing. Allegations of research misconduct may come from researchers or managers within UCL or from outside UCL. Allegations made anonymously or pseudonymously may be considered under the procedure. All allegations are treated confidentially while they are under consideration.

In terms of process an initial assessment is undertaken by the Registrar to establish the nature of the allegations, to establish whether they are vexatious or malicious, whether they fall within the definition of research misconduct or constitute some other form of misconduct, and whether there is any immediate risk of harm to anyone that requires intervention.

The initial assessment stage should be completed within 20 working days.

Allegations that are found to fall within the remit of the academic research misconduct procedure will proceed to the Screening Stage. The Respondent will be notified by the Registrar, usually in person, that allegations have been made and what steps are to be taken under the academic research misconduct procedure. The screening stage should be completed and a report delivered within 45 working days.

The Screening Panel will determine whether the allegations of misconduct in research:

- are mistaken, frivolous, vexatious and/or malicious;
- have some substance but due to a lack of intent to deceive or due to their relatively minor nature, should be addressed through education and training or other non-disciplinary approach rather than through the next stage of the Procedure or other formal proceedings; or
- are sufficiently serious and have sufficient substance to justify a Formal Investigation; or
- where the Screening Panel finds no prima facia evidence of misconduct in academic research, however there is evidence of potential misconduct that is not research misconduct, that the case should be referred directly to UCL’s relevant disciplinary process or another internal process.
Where a 'Formal Investigation' is instituted the investigation panel will typically be appointed within 30 working days. The duration of the Formal Investigation is without time limit. The Investigation Panel will produce a report that:

- summarises the conduct of the investigation;
- states whether the allegations of misconduct in research have been upheld (in whole or in part) or not upheld, giving the reasons for its decision and recording any differing views;
- makes recommendations in relation to any matters relating to any other misconduct identified during the investigation; and
- addresses any procedural matters that the investigation has brought to light within UCL and relevant partner organisations and/or funding bodies.

4.3.2 Investigations into Research Integrity

There have been three investigations into research integrity germane to the focus of this Inquiry:

Investigation 1 - 3rd Jan 2015 Professor Pierre Delaere against Professors Birchall, Macchiarini and Seifalian consisting of an unpublished document entitled "Stem Cells can regenerate the windpipe and other (hollow) organs. The biggest lie in Medical History?" This document was also sent to The Lancet and the Karolinska institute. UCL Screening panel examined the evidence on 22nd April, 8th May, and 21st May 2015. It found that the allegations against Professor Seifalian had no substance and those against Professor Birchall had some substance in that there was a misleading statement in a 2012 Lancet paper but that there was no evidence of intent to deceive.

Investigation 2 - 10th March 2015 Professor Mark Emberton against Professor Seifalian alleging a lack of appropriate ethics permissions for the work he had carried out in 2013/14 where POSS-PCU constructs were implanted into the post-auricular region in patients. The Screening Panel investigation examined the evidence on 1st February and 21st March 2016 and having found that the allegations were sufficiently serious and had sufficient substance recommended a Formal Investigation in August 2016. The Formal Investigation has not yet taken place.

Investigation 3 - 19th June 2015 Anonymous vs Professor Seifalian and Professor Gaetano Burriesci (via The Wellcome Trust). Professor Alexander Seifalian and Professor Gaetano Burriesci held a Translation Award funded by The Wellcome Trust titled "Development of a novel artificial aortic valve for transcatheter implantation". In June 2015 The Wellcome Trust received a letter making anonymous allegations of research misconduct against Professors Seifalian and Burriesci and notified UCL Academic Services Office of this on 19th June 2015. The allegations were broad ranging. This case was referred to a Screening Panel investigation which, in late summer 2016, found that the allegations made against the respondents should not be upheld and should be dismissed.

The author of the allegations was aware that Professor Seifalian had been suspended and described this as being "shrouded in secrecy". He or she expressly stated that Professor Seifalian had left UCL “due to gross academic misconduct”, when in fact this was not the case.
Around the same time Professor Alexander Seifalian and Professor George Hamilton held another Translation Award funded by The Wellcome Trust titled "A clinical study to assess the safety and efficacy of POSS-PCU small diameter grafts in arteriovenous access and coronary artery bypass graft (CABG) surgery". Although no specific allegations of research misconduct had been made, the anonymous allegations referred to in Investigation 3 prompted The Wellcome Trust to raise concerns with UCL in July 2016 about the use of POSS-PCU small diameter grafts in this study. An internal review by UCL identified instances of possible research misconduct by Professor Seifalian and recommended in September 2016 that a formal allegation of research misconduct should be made against him. It also recommended that the clinical trial should not proceed as planned. A Screening Panel has not yet been appointed to review that formal allegation of research misconduct.

In addition Professor Seifalian was a co-investigator on a Translation Award number 106574/Z/14/Z entitled "Soft robotic total larynx replacement" the Principal investigator for this grant was Professor Martin Birchall. This grant had been awarded, work is ongoing and may proceed to in vivo animal studies in the next few years.

The Wellcome Trust

The terms and conditions of awards from The Wellcome Trust required the organisation which has been awarded a grant to notify the trust of any change of circumstances of the award holder including suspension. UCL did not notify The Wellcome Trust that Professor Seifalian had been suspended until The Wellcome Trust directly requested this information. UCL declined to give The Wellcome Trust information regarding the circumstances of Professor Seifalian's suspension. The Inquiry were told that the reason for this was that the suspension was on account of allegations of financial fraud and misconduct not relating to research activity. The Wellcome Trust considered this a breach of their terms and conditions and made the following formal requests:

a) Confirmation that the allegations of research misconduct made against Professor Seifalian were being investigated, the course of action being followed and the expected date of the conclusion of the investigation.

b) Notification of who would take over activities and responsibilities of Professor Seifalian as co-principal investigator on the aforementioned Award 1 and as co-investigator on Awards 2 and 3, such nominees to be agreed by The Wellcome Trust.

c) Confirmation that UCL was communicating with all parties on the aforementioned Awards 1-3 with regards to Professor Seifalian’s situation.

On direct enquiry of Dr Alysson Fox representing The Wellcome Trust it became clear that the Trust had held concerns over the reasons for Professor Seifalian's suspension and concerns over the impact of his suspension on the ability of the research group to continue with and deliver the research programmes encompassed by the grants. UCL did not notify The Wellcome Trust of the reasons for his suspension. This was because he had been suspended pending investigations into allegations of financial irregularities and not because of any allegations of research misconduct. There appears to have been a belief within the faculty that it would be inappropriate and perhaps illegal to share this information with The Wellcome Trust at this time. The communication between UCL and The Wellcome Trust over the reasons for Professor Seifalian's suspension were therefore slow and lacking content, which led to a degree of frustration on behalf of The Wellcome Trust.
The Inquiry considered that UCL did have a contractual responsibility to inform The Wellcome Trust of the suspension of Professor Seifalian and that it could have done so in confidence. It was also felt that there could have been better communication between UCL and The Wellcome Trust over the circumstances of the suspension, timeline of investigation and interim arrangements without compromising Professor Seifalian’s rights.

Medical Research Council (MRC)
The MRC were contacted by Professor Martin Birchall in his role as principal investigator of the Regenvox trial and were told that the trial had been suspended by UCL as a consequence of the ongoing Inquiry into regenerative medicine research at UCL. Professor Birchall had been informed by Professor Tarek Yousry and by Professor Tony Mundy that they had decided to suspend recruitment of patients to the Regenvox trial pending the outcome of the UCL Inquiry. The MRC requested information from the Inquiry directly and was informed by the Chair that the decision to suspend the trial had been made by UCL and was not a decision made by the Inquiry. Dr Catriona Crombie was invited to attend the Inquiry to represent the MRC so that this could be more fully explained. The principal concerns of the MRC were firstly that patients might be disadvantaged. Secondly, that the period of trial suspension had not been made clear to them by UCL and that while the grant was suspended the research would not be progressed and any salaries dependent on the grant might be affected. Thirdly that the information of the trial suspension had been received second hand, rather than directly from UCL. With respect to the first point, Professor Emma Morris Co-Chair of the Cell, Gene and Regenerative Medicine Network at UCL, made enquiries and confirmed that there was only one patient who was affected by the suspension of the Regenvox trial and that this patient would not be significantly disadvantaged by the trial suspension. Dr Crombie was informed by the Chair that the inquiry was due to report at the end of June or early July 2017 but that any decision regarding trial suspension was at the discretion of the UCLH Safety Committee. She was also informed that the responsibility for communication with the MRC lay with the grant holder, in this case UCL.

The Inquiry considered that UCL had a responsibility under the terms and conditions of the MRC award of the Regenvox trial to notify the MRC of the trial suspension and the reasons for this in a timely manner.

4.4 Conclusions

The Inquiry considered that the Centre for Cell, Gene and Tissue holds all relevant authorisations under the relevant legislation for Cell and Tissue processing and ATMP manufacture. However, it was of the view that there is no evidence that Professor Seifalian’s research laboratory used for manufacture of the POSS-PCU constructs met the requirements of the Medical Devices Regulations 2002 or the ATMP legislation. This is a matter of significant concern, both for the constructs intended for clinical use as medical devices as well as those intended for incorporation into combination advanced therapy medicinal products.

The Inquiry considered that UCL has a robust governance structure for patients who are treated in clinical trials.

The governance structure for patients who are treated as compassionate use or exceptional use cases differs from clinical trials. The Inquiry considered that the Clinical Ethics Service
(CES) team based at Great Ormond Street Hospital was a highly professional and well-structured team with clear lines of reporting and standards for operating. The Inquiry had confidence that the cases of children considered by the CES were well represented and that the CES enabled children and their parents to reach difficult decisions about treatment choices in an informed and shared decision making way.

The Inquiry heard evidence that the cases of adults considered to need compassionate use or exceptional use treatments at UCLH were considered by an ad hoc committee of three senior clinicians. In practice often only one member of this ad hoc committee would be an expert in the field and could on occasion exert significant influence the other committee members. External opinion was sometimes but not always requested. This committee did not routinely contain specialists in bioethics. Although not falling directly within the Inquiry's Terms of Reference, the Inquiry noted that the process employed by GOSH to consider compassionate or exceptional use treatments was more robust than that employed by UCLH and that UCLH would benefit from adopting a process similar to that employed by GOSH. Indeed the Inquiry team believed that a single unified model should be employed across UCLP hospitals.

The Inquiry found that UCL's current "Procedure for investigating and resolving allegations of misconduct in academic research", which became effective on 1st January 2017, provides a robust structure for investigation that is timely, appropriate and fair to both the respondent and the individual alleging research misconduct.

All of the research misconduct investigations into Professor Seifalian and members of the tracheal transplant research group that were studied by the Inquiry pre-date the current procedure. The Inquiry found, in particular, that there were significant delays in the process of conducting Investigations 2 and 3. In relation to Investigation 2, whilst the "Initial Assessment" was timely, the Screening Panel stage was very detailed and lasted many months. The original allegation was made in March 2015 and it was not until August 2016 that the Screening Panel recommended that a Formal Investigation be conducted. In relation to Investigation 3, the original anonymous allegation was notified to UCL in June 2015 but it was not until September 2016 that the Screening Panel recommended that the allegations should not be upheld and should be dismissed. The Inquiry team felt that such protracted initial investigations run the risk of placing unrealistic delay on research projects (which may be suspended pending the result of the investigation) and equally create problems for grant funding agencies. The review process from receipt of an allegation through to the end of the Screening Panel is simply there to establish whether there is a prima facie case to answer. It should, therefore, be conducted with a light touch. UCL's current procedure contemplates that the Initial Assessment should "normally be completed within a maximum of 20 working days from the receipt of the allegations" and that the Screening Panel should "aim to complete its work within 45 working days". The Inquiry team believe that, in fairness to all concerned, every effort should be made fall within these time limits. If there is a prima facie case to answer, the detailed investigation should, properly, be conducted by the Formal Investigation Panel.

Each of the Screening Panels appointed for the investigations studied by the Inquiry were comprised entirely of UCL personnel. Only involving UCL personnel in Screening Panel investigations protects, to some extent, the rights of the Respondent by maintaining a greater degree of confidentiality but it also raises the possibility of criticism for lack of
transparency, perceived conflict of interest and lack of independent objectivity. Whilst it would not be appropriate in all cases, in very serious and/or potentially high profile cases the Inquiry recommends appointing an independent Chair to the Screening Panel.

The Inquiry found evidence that communication to funders of the process and progress of research misconduct investigations was, on occasion, slow or insufficient. Similarly, there appeared to be a misunderstanding within UCL regarding the need to communicate with relevant funding agencies where investigations were being conducted in relation to allegations that fell outside the research misconduct procedure.
Chapter 5: Relationship between UCL, Paolo Macchiarini and the Karolinska Institute

5.1 Development of a Research Collaboration

Paolo Macchiarini graduated in medicine from the University of Pisa in 1986 and undertook a Master of Surgery in 1991 also from the University of Pisa. He undertook a Master of Science degree in Organ and Tissue transplantation at the University Franche-Comté at Besançon, France between 1992 and 1994 and then a PhD also in Organ and Tissue transplantation at the same University completing his thesis in 1997. During his PhD studies he had undertaken research into pig tracheal transplantation using an allograft model in pigs with reportedly good outcomes. In 1997 he met Dr Martin Birchall who had been developing research into laryngeal transplantation at the University of Bristol. Dr Macchiarini was appointed as a Senior Lecturer at Paris Sud Université and Dr Birchall had also been appointed as a Senior Lecturer at the University of Bristol.

During the Inquiry Professor Birchall described himself as being frustrated at the time that laryngectomy was the only procedure available for certain conditions of the larynx and he became interested in the concept of laryngeal transplantation. He undertook experiments in animals to address the questions of restoring nerve function following laryngeal transplantation and also controlling the immune response to a laryngeal graft. Dr Birchall had heard of the research conducted by Dr Macchiarini in Paris and organized to visit him there. Drs Macchiarini and Birchall worked together to develop an allograft model of laryngeal transplantation in the pig. This model formed the basis of a successful Wellcome Trust Intermediate Fellowship application by Dr Birchall. Thereafter and for the next 10 years the two met one to two times per year at meetings and discussed similar research aims. During the tenure of Dr Birchall's 5-year Wellcome Trust Fellowship, Dr Macchiarini would visit Bristol periodically to help with aspects of the porcine surgery since Dr Birchall was an Ear, Nose and Throat specialist (ENT) and was not a thoracic surgeon like Dr Macchiarini.

Dr Birchall was contacted by Dr Macchiarini in 2008 for assistance in the organisation of a transplant using a decellularised cadaveric trachea in a woman with tuberculous stenosis and scarring of her left main bronchus (Patient A). The specific role requested of Dr Birchall and his colleague Dr Anthony Hollander at the University of Bristol was to prepare epithelial cells (Dr Birchall) and chondrocytes (Dr Hollander) to be transferred to Barcelona to enable seeding of a decellularised tracheal graft which had been prepared there. Professor Birchall 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. The operation proceeded and involved the replacement of the left main bronchus of the woman with a section of the seeded decellularised cadaveric trachea. The procedure was declared an early technical success. The case received substantial media and scientific coverage and was lauded as a major step in the development of regenerative medicine.
5.2 Recruitment by UCL

In 2009 Dr Birchall was recruited to UCL from Bristol and he was appointed as Professor of ENT Surgery with laboratory space at the Ear Institute and also at the Royal Free Hospital (RFH). Not long after his arrival in London he recommended to Professor David McAlpine, then Director of the Ear Institute at UCL, that Dr Macchiarini should be offered an honorary professorship. Professor Birchall arranged for Dr Macchiarini to meet Professor McAlpine, though Professor Macchiarini said in his submission to the Inquiry that he did not know that, at the time. This was because UCL were planning to offer him an honorary professorship. The principal reason for suggesting this appointment was to strengthen a research collaboration and major grant application ($20 Million) that was planned to the California Institute of Regenerative Medicine by the Ear Institute. Professor McAlpine requested that the appointment be expedited to meet the timeline of the grant. The term of appointment was 5 years between 1st August 2009 and 31st July 2014.

The appointment was approved by UCL and Professor McAlpine notified Professor Macchiarini of this in a letter dated 25th August 2009. The appointment of visiting or honorary professor was a research appointment but did not allow clinical practice and was not a remunerated appointment. Professor Macchiarini was given a UCL email address and access to the university library and online resources. Professor Macchiarini has confirmed that his association with UCL at that time was an intellectual contribution to grant applications, laboratory meetings and preclinical projects and multidisciplinary clinical conferences. He also confirmed that this did not confer any clinical privilege at UCL and was a non-remunerated appointment.

Also in 2009, a separate attempt was made by UCL to formally recruit Professor Macchiarini on a substantive contract as a member of staff using the Exceptional Talent Recruitment Scheme offered at that time by the Medical Research Council (MRC). This scheme was designed to support talented academics usually from overseas but exceptionally from within the UK by providing funding to enable the individual to re-establish their programme of work while applying for substantive grant funding at their new institution. The application submitted by UCL on behalf of Professor Macchiarini made a case for development of regenerative medicine therapy. It was reviewed by the MRC and whilst they found that this was an area of strategic importance and that Professor Macchiarini had a track record of funding in this area and the surgical ability to drive the translational side of a programme of work, they also felt, that his scientific interest and experience in the basic science aspect of the grant was weak and that his ability to be successful in securing a substantive portfolio of funding was less convincing. On this basis the grant application was declined.

On the clinical side Professor Chris McGregor, then Professor of Cardiac Surgery at UCL (now retired) had raised concerns related to a rapid succession of jobs held by Professor Macchiarini with absence of available references. Other individuals questioned whether Professor Macchiarini would fit in with the system of working within UCLH. On the basis of the unsuccessful bid to the MRC for financial support for recruitment and the lack of strong support from UCL associated clinicians, the potential substantive appointment of Professor Macchiarini was not progressed though he did continue with his honorary Professorship at UCL.
5.3 Clinical Cases related to UCL

This is a brief summary of the 4 cases in which Professor Macchiarini was involved with individuals at UCL. Each case is discussed in more detail in Chapter 7.

Professor Birchall had assisted Professor Macchiarini by preparing epithelial cells at the University of Bristol which were seeded on to a cadaveric decellularised tracheal scaffold in Barcelona which was subsequently transplanted into Patient A in 2008 to reconstruct a chronically stenosed bronchus secondary to tuberculosis. Professor Macchiarini moved to the Karolinska Institute towards the end of 2010 but retained his honorary Professorship with UCL. Relations between Professors Macchiarini and Birchall had deteriorated and they did not work together on any projects after this time. Professor Macchiarini established a research collaboration with Professor Alexander Seifalian, a biomaterials scientist employed at the RFH campus by UCL. Professor Macchiarini requested Professor Seifalian to make a synthetic trachea using a compound that Professor Seifalian had been developing for vascular surgical applications called POSS-PCU. Neither Professor Birchall nor any of the clinical team involved with complex airway management were involved in this project. The synthetic trachea was manufactured in London and transported to Sweden and was the first synthetic tracheal transplant performed at the Karolinska Institute by Professor Macchiarini - the recipient was a 36-year-old Eritrean man resident as a student in Iceland (Patient B).

Professor Macchiarini was involved in the planning and surgery of a paediatric patient (Patient D) at GOSH with Professor Birchall and Professor Martin Elliott. This case also received significant publicity and on this occasion, most of the plaudits were directed towards the local team, which was reported to have caused some friction with Professor Macchiarini.

Not long after, a young woman (Patient C) was referred to Professor Macchiarini at the Careggi Hospital in Florence by Mr Paul O’Flynn for consideration of a tracheal transplant. This was performed in Florence in July 2010.

Professor Macchiarini was not directly involved in any of the further transplants performed in London.

5.4 Arguments over Patents and Intellectual Property

In July 2011 Harvard Apparatus Regenerative Technology (HART) filed a US patent (provisional application number 61/505096) in their own name and naming the inventors as Professor Macchiarini and Professor Seifalian. This application claimed for a method of producing a synthetic scaffold for replacing an airway or portion thereof and a method of seeding a synthetic airway scaffold. This application was based on a POSS-PCU scaffold and did not acknowledge that UCLB already had a pre-existing patent US80008023164, titled "Polymer for use in conduits medical devices and surface modification". It is claimed that HART did not seek UCLB’s consent before filing their patent, despite UCLB having an evident interest in this subject matter.

UCLB claimed for majority intellectual property ownership in US priority patent application number 61/505096 and as holders of background intellectual property to the POSS-PCU

1 See Section 7.6
2 See Section 7.4
polymer material on which this application was based. Professor Macchiarini was requested by UCLB to assign rights in the application to UCLB prior to the application reaching the Patent Co-operation Treaty (PCT) stage on the anniversary of its initial submission, (PCT stage 6 July 2012) in exchange for a pre-agreed share of any revenues generated through commercialisation of any patented subject matter. Professor Macchiarini disputed his minority stake and refused to assign his rights in the patent to UCLB. This reportedly caused hostility and a deterioration in the relationship between Professor Macchiarini and UCLB.

A compromise agreement was reached between Professor Macchiarini and UCLB in advance of the PCT stage of US priority patent application number 61/505096 to file a further patent 13/542218 on 5th July 2012 which claimed priority from the aforementioned patent application 61/505096. This named Professors Macchiarini and Seifalian as co-inventors and UCLB and HART as applicants.

UCLB also simultaneously filed the same specification as a “placemarker” naming Professor Seifalian as the sole inventor and UCLB as the sole applicant. This simultaneous submission was designed to protect UCLB's position on the patent and was undertaken on the advice of the law firm Vedder Price LLP who were acting on UCLB's behalf. PCT/US12/45721 was filed on 6 July 2012 preserving all right from the US priority patent application number 61/505096 predicated on reaching agreement between the involved parties on inventorship, ownership and control within a stipulated time frame through good faith discussion.

A restriction requirement issued by the US Patent and Trademark Office on 4 October 2013 determined that the claimed subject matter of US Patent application number 13/542218 comprised several distinct inventions:

1. Claims 1-4 drawn to a synthetic scaffold,
2. Claims 5-9 drawn to a method for making a scaffold,
3. Claim 10 drawn to a method of seeding a scaffold; and

The issues restriction requirement further requested that in accordance with patent law, each invention be prosecuted under a single application through the election of a single invention for continued prosecution of the existing application with remaining subject matter protected as necessary in the form of new separate continuation patent applications.

Professor Macchiarini was not a co-inventor with Professor Seifalian on the invention groups 1 and 2 and could only be a co-inventor on group 3. UCLB proposed that group 3 (claim 10 drawn to a method of seeding a scaffold) should be elected in response to the restriction requirement for the continued prosecution of US patent application number 13/542218. After much deliberation with Professor Macchiarini and HART rejecting the assertion that they had no claim to inventorship on invention groups 1 and 2 it was agreed that invention group 3 was elected for continued prosecution. Professor Macchiarini and HART upheld their view to their claim of inventorship of invention groups 1 and 2.

Invention group 3 was subsequently elected with traverse for the continued prosecution of US patent application number 13/542218 but was ultimately abandoned and the subject matter claimed for in new US continuation patent application number 14/484178 filed on 11 September 2014 with Professors Seifalian and Macchiarini named as inventors and HART and UCLB as named applicants.
According to his own testimony and supporting documentation Professor Macchiarini transferred his share of the patent to Harvard Apparatus Regenerative Technology (the manufacturers of the Bioreactor) in return for a $5000 donation to a children's charity in Hannover. The Inquiry has seen evidence confirming this from HART and indicating that Professor Macchiarini did not receive any direct payment from them and also evidence from the children's charity Lions Forderverein Hannover-Aegidius acknowledging receipt of the donation.

5.5 The End of the Relationship

In early 2012 the tracheal research group at UCL received news that Professor Macchiarini had undertaken what was described as the first nanofiber tracheal transplant in the Karolinska Institute via a press release from the synthetic trachea manufacturer. This used a different material from POSS-PCU and was manufactured by an American supplier Nanofiber Solutions and the transplant was performed on a US citizen in Stockholm. He died within weeks of the transplant. Professor Seifalian and others at UCL were unaware that Professor Macchiarini had developed a new collaboration and he had not told them of this new partnership. The collaborative relationship between Professor Macchiarini and individuals employed by UCL had effectively broken down completely by late 2012. The dispute over patents, inventorship and intellectual property soured the relationship and reports reached researchers at UCL that Professor Macchiarini was actively seeking other manufacturers and suppliers of polymeric scaffolds. Professor Macchiarini gave evidence to the Inquiry to the effect that he considered that the focus on commercial aspects of the project by UCLB and Professor Seifalian was at least partly responsible for the breakdown in relations between Professor Macchiarini and the UCL airway research team. Professor Seifalian was not requested to manufacture any further tracheas for Professor Macchiarini and all subsequent synthetic tracheas transplanted by Professor Macchiarini were made by other manufacturers and suppliers who were not connected with UCL and relations with UCL became infrequent. Professor Macchiarini provided evidence to the Inquiry that the decision to use synthetic tracheas from other manufacturers was based only on clinical considerations.

Paradoxically, Professor Seifalian did participate in a large European programme grant led by Professor Macchiarini entitled 'Biomaterials for tracheal replacement in age related cancer via a humanly engineered airway' (BIOtrachea) which commenced in April 2012 and involved 11 other European investigators.

Professor Macchiarini’s honorary professorship expired on 31st July 2014 and no application was made to extend or renew this arrangement. By coincidence the first of two research misconduct allegations was filed at the Karolinska Institute in June and August 2014 and shortly after this the extent of the adverse outcomes associated with Professor Macchiarini’s tracheal transplant programme became public knowledge.

In August 2014 the European Commission suspended the BIOtrachea grant on the grounds that the work package lead by Professor Seifalian had not met expectations in terms of deliverables and outcomes. Following further correspondence and a highly critical report from another member of the consortium concerning the quality of manufacture of POSS-PCU tracheas, the BIOtrachea programme was formally terminated with effect from the end of April 2015.
5.6 Conclusions

Honorary contracts are common means of engaging with individuals employed by other organisations but who have interest or involvement with the awarding University. They are often awarded to support teaching and research activities and can be awarded at different levels of the academic scale. The award of an honorary appointment by a University is often considered to be a mark of prestige or achievement. Since honorary contracts are rarely remunerated they are often considered to be of lower importance than other contracts. The Inquiry reviewed the UCL procedure for the award of honorary academic contracts and found it to be similar to that of other Universities. In the specific case of Professor Macchiarini his honorary professorship was awarded principally to foster research collaborations between him and other workers at UCL. The submission process involved the submission of a letter from the Director of the Institute where he was to be affiliated, - in this case the Ear Institute - and a copy of Professor Macchiarini's Curriculum Vitae (CV). It has been alleged in the media that aspects of Professor Macchiarini's CV may have been misrepresented, particularly his explanation of Privat Dozent and Recherche Habilitation as indicating a full Professorship when neither term has this meaning. However, the CV was not the only consideration in the application for the award of an honorary professorship and his reputation, recommendations and publication record were also taken into account. The Inquiry concluded that the scrutiny and application process for Professor Macchiarini’s honorary appointment was not sufficiently thorough and would have benefited from a requirement to obtain external referees.

An honorary appointment with a university entitles the holder to certain rights and privileges and in turn carries a responsibility on the holder to abide by the terms and conditions of the University. It is assumed that the honorary appointment of an individual would carry a low risk but in the case of Professor Macchiarini it has undoubtedly caused some reputational harm to UCL. The Inquiry considered that the specific reputational risk to an organisation of awarding an honorary contract should be considered as part of the process of appointment in the same way that the benefits of the appointment are also considered.

For clinical academics the potential to cause injury to patients may have liability issues for the host organisation if such injury occurs during part of their activities under an honorary contract. For this reason the Inquiry considered that it may be appropriate to either have different types of honorary contract or to specify the nature of the engagement with the university which is covered by the honorary contract.

The Inquiry also considered that the establishment of specific terms of engagement between the University and the honorary appointee would permit termination of the appointment by the University if appropriate.
Chapter 6: POSS-PCU

6.1 POSS-PCU Development Overview

George Hamilton, Professor of Vascular Surgery at the Royal Free Hospital had a longstanding research interest in developing better quality artificial grafts for use in arterial disease that would have the same or better characteristics than autologous vein grafts, which were the best available material at the time. The concept was to develop a synthetic graft, which had inherent elasticity as it was believed that the relatively high failure rates and short patency times of other synthetic materials such as PTFE and Dacron were in part due to their inelasticity. Professor Hamilton developed a research interest and collaboration with Professor Seifalian, which dated back to 1988/1989.

Alexander Seifalian undertook a degree in nuclear physics at King's College London. Following this he worked at CERN for a period but left that position and worked in the City of London in the financial sector for a while. He decided to return to University and undertook a Master of Science degree in biophysics at the University of London. He then worked in Manchester for a period undertaking research into temporo-mandibular joint dysfunction. Following this he returned to London and took a job working in the Department of Nuclear Medicine at the Royal Free Hospital. Here he was looking at myocardial dysfunction and working as a technician on isotope scans. He then took a research post looking at ischemia reperfusion injury and haemodynamics. He went to work at Harvard for 6 months in a cancer biology laboratory and then returned to the Royal Free Hospital. He undertook a PhD at the Royal Free Hospital in isotope based cardiac imaging. He travelled to USA, Sweden and Japan with research posts before returning once again to London. He then decided to enrol in evening classes at the London Polytechnic (as it was then called) and began to learn about polymer chemistry. He was still working at the Royal Free Hospital at this time and began to work with Professor George Hamilton in the haemodynamics laboratory. He began to apply his newly learnt knowledge of polymer chemistry to research questions and became interested in the field of nanotechnology. Alexander Seifalian was not therefore a formally trained polymer chemist or biomaterial scientist but was involved in research in imaging and shared an interest in vascular dynamics.

In the 1990s Professors Hamilton and Seifalian obtained funding to develop composite vascular grafts using a very light Dacron backbone to give structural integrity to a graft which was populated with autologous expanded smooth muscle cells and subsequently endothelial cells from young pigs. These grafts were used in the pig to replace sections of the aorta and functioned relatively well. Experiments started using human cells. The group found that they were unable to expand endothelial cells from elderly adults (the population in humans who have vascular disease) and they struggled to translate the technology. On the basis of this series of experiments a decision was taken by Professors Hamilton and Seifalian to concentrate on creating a fully synthetic arterial graft.

There had been interest from other researchers in polyurethane as a possible material for vascular grafts because of its elastic properties. Previous research had identified a problem around the susceptibility of the soft component of the polymer to hydrolytic and oxidative stress, which had the clinical effect of making the grafts aneurysmal. Professors Hamilton and Seifalian investigated the polyurethane family and found one polymer, which appeared to have more favourable characteristics, and they called this material Compliant
Polyurethane or CPU. This material contained polycarbonate urea and this had greater resistance to hydrolytic and oxidative stress and retained its compliance even after long periods of testing. The technology was bought out by Le Maitre who developed a clinical graft although Professors Hamilton and Seifalian warned them that it was still thrombogenic. The product called "Expedial" was later withdrawn from the market. Le Maitre had previously agreed to fund research into making the inner lining of the graft less thrombogenic but this arrangement did not continue. Professors Hamilton and Seifalian decided to try to make a new polymer and enlisted the help of an experienced polymer chemist Hendrick Savoginski. They added a siloxane cage structure known as POSS to the CPU to make POSS-PCU. They repeated all of their original experiments and found that the POSS-PCU compound had similar compliance and resistance to stress as CPU but had reduced thrombogenic potential. This was in 2004-2005 and since the chemical composition of the compound was novel it was possible to apply for a patent.

6.2 Information Provided in the Patents

The POSS-PCU polymer concept embodies a set of rational polymer design steps, aimed at improving the performance of conventional polyurethanes as implant materials. The functional aim, served by the design, was to create an implant material family capable of better cell adhesion, greater mechanical strength and resistance to micro-scale disruption and fracture and thereby also reduced biodegradation. The first step in this concept was to incorporate low biodegradation polyol polycarbonate as the soft segment of the polyurethane; this would give resistance to the material from inward movement of solute from the biological environment. Polycarbonate is known to be relatively resistant to hydrolysis. The second step was to introduce a siloxane side group to the polymer chain backbone in order to create a nanoscale particulate phase that acted as a hard segment component that could possibly reduce surface blood coagulation and enhance endothelial cell growth. For this there was a shift from linear chain siloxanes to siloxane nanocages. These were also better able to resist micro-domain movement inside of the material and so protect from the micro-fractures that could then for example cause damage through facilitated solute entry. The published patents make clear the steps and also provide data on the enhanced strength of the resulting material POSS-PCU (US 2008/0233164 A1; WO2005/070988 A1).

The Inquiry noted that these patents therefore mainly present chemical strategies, so evidence for use of the material as an implant is not given.

6.3 Translational Evidence for POSS-PCU

The Inquiry explored the clinical use of POSS-PCU as a tracheal implant considering the underpinning biological (in vitro and in vivo) evidence and the translational routes to clinic.

The Inquiry concluded that POSS-PCU was designed as a rational answer to the problem of traditional polyurethanes as biomaterials. The polymer was aimed at improving degradation stability, improved mechanics and better cell adhesion based on a surface nanotopography.

6.3.1 Translational Evidence for the use of POSS-PCU in Cardiovascular Surgery

As previously noted POSS-PCU was originally designed as a stent material for small diameter blood vessels. The design advance at this stage was the creation of stents with porous walls that connected to the lumen. This allowed a better approximation to natural blood vessel
mechanics and thereby improved blood flow dynamics, an apparent basis for improving sustained endothelial attachment. The open pore network also allowed for blood uptake from the lumen to create a biohybrid structure. Various cell biological studies, including affinity molecule functionalisation, were carried out with the aim to optimise endothelial attachment and/or capture.

There was evidence provided of a robust translational programme with rigorous in vitro and in vivo small animal studies leading to a preclinical large animal sheep trial funded by a Wellcome Trust grant (Preclinical assessment of small diameter conduit made from a nanocomposite polymer for coronary artery bypass graft application). This trial was carried out under Good Laboratory Practice (GLP) by the Northwick Park Institute of Medical Research between June 2010 and May 2011. The Institute is a certified independent contract research organisation conducting work based on the principles of GLP as adopted by the Organisation for Economic Cooperation and Development (ENV/MC/CHEM (98) 17 in conformity with the requirements of Directives 2004/09/EC and 200/10/EC, and was used to ensure that the results were externally validated. The data demonstrated improved haemocompatibility with the porous material, as evidenced by reduced platelet activation. Some evidence for translation of the advantages seen in vitro to the in vivo situation was seen following use of the material as carotid artery stents. The one study reported is limited in scope, and uses 11 implants in sheep for 9 months. There was retention of stent patency in 7 out of 11 carotid implants. A key finding was the lack of endothelialisation despite the early emphasis on improved biomaterials in the early in vitro studies. In addition, there was a study of tissue implanted POSS-PCU solid sheets. The implant site showed no evidence of past or ongoing inflammation or of capsule formation, at 36 months, at least at the gross level. The contrast with an equivalent material that had linear silicone side chains instead of silicone nanocages was stark; the former provoked a substantial inflammatory response. The hypothesis was that the higher fibrinogen content at the POSS-PCU surface was different through denaturation and that this resulted in a reduced inflammatory response.

The combination of in vitro and in vivo studies allow for the conclusion that POSS-PCU is degradation resistance and has high mechanical strength. There is clear evidence that modified material through pore creation can make stents more compliant and potentially usable for small blood vessel replacement. However, the evidence that endothelialisation can occur is absent from in vivo studies.

These data provided the basis of an application to the MHRA for a vascular graft / coronary bypass graft clinical trial which has been approved but not commenced (CI-2015-0043).

Reference is made in the Tracheal Transplant Protocol submitted to the Karolinska Institute Ethics Committee of an 18cm POSS-PCU graft implanted into a human to replace the femoral artery. Professor George Hamilton testified that this had only recently come to his attention, that the patient was a 26 year old male drug addict and it was performed in Tehran for a bypass of the common femoral artery which had become chronically infected and aneurysmal. He stressed that this was undertaken without his knowledge, opinion or consent and offered the opinion that using a prosthetic polymer bypass graft in an infected vascular bed is clinically negligent because of the inevitable contamination resulting in spreading infection, the need for removal of the graft and significant incidence of major lower limb amputation and death. No information or data relating to this patient in terms of outcome has been seen by the Inquiry. The construct was most likely manufactured by
Professor Seifalian’s laboratory, and may have been part of a batch of grafts sent to Tehran for implantation in sheep. There is no evidence that this construct was manufactured to GMP in compliance with the Medical Devices Regulations 2002 exceptional use provisions. UCLB indicated that they were not aware that a POSS-PCU construct had been administered to this patient and no MTA had been released for this purpose.

6.3.2 Translational Evidence for the use of POSS-PCU in Tracheal Replacement Surgery

The poragen defined POSS-PCU model for tracheal replacement appears to be a larger scale version of the porous small blood vessel stent concept with limited development for a tracheal tissue. The method of casting and fabrication has similarities, not least the choice of leachable salt crystals to create the pores. However, in contrast to the vascular stents, whilst there was connectivity to the luminal surface, a dual scale pore structure was incorporated. Using larger crystalline material (sucrose), large connected pores were created within the bulk of the tracheal replacement structure, and these extended to the outer (abluminal) surface to provide continuity for tissue ingrowth for regeneration of tracheal cartilage. Small pore structures were incorporated into the dense luminal surface. It was correctly deduced that in the absence of surface porosity, it would not be possible to maintain the growth of respiratory epithelium, given that nutrient support could only arise from the subjacent surface and through the tissue that would grow in from the outer surface of the tracheal tube. The challenge to such an arrangement was balancing the need for a high surface porosity to ensure cell viability on the luminal surface and a low porosity to maintain mechanical integrity. There is limited analysis of the balance of the two factors in the published works and the use of salt poragens for manufacturing is known to be very variable. One correlate was confirmed, however, that if large pores were used to host an epithelial layer, then the result was a cellular clustering within the pores and a complete absence of cell continuity. Even with the small pores, there was no evidence of a continuous epithelial layer on scanning electron microscopy. It is also of note that the epithelial culture work was done in growth medium and not at a liquid-air interface, so limited conclusions if any could be reached about outcomes in vivo.

The Inquiry felt key experiments were lacking to define the material as a suitable implant for clinical trial. From the standpoint of a viable epithelium it was vitally important to know what nutrient, oxygen and other solute fluxes there would be through the porous wall structure. There is no evidence of an investigation of (i) diffusive mass transport and (ii) an air interface bioreactor analogous to the organotypic cultures used for the study of skin models. In lieu of this, studies were limited to observing hydraulic permeability across the wall of the tracheal model. This demonstrated pore connectivity, but provided no information on the adequacy of nutrient supply or diffusivity.

There was clear evidence that growth on the outer surfaces (abluminal) occurred over time but the proof of cartilage formation was weak and lacking. The in vitro protocol for seeding either the luminal or external surface of the porous POSS-PCU lacked the experimental evidence for creation of a tracheal tissue with the formation of cartilage, endothelial, or epithelial layers.

No evidence was supplied of microbial studies, specifically of low levels of microbial surface contamination or a reduction in microbial entry through the implant which can lead to an infective stimulus and damage. The intended site of placement of tracheal POSS-PCU
constructs was at an air tissue interface and this is considered in microbiological terms to be a dirty environment.

In addition to degradation resistance, a feature of the POSS-PCU was its mechanical strength. Whilst there was evaluation of the mechanical strength of the material and its confirmed superiority of strength, there had been no consideration of what the mechanical match to natural trachea needed to be. A compliance mismatch here coupled with the relative motion of natural and polymeric material could lead to localised tissue damage.

Standard autoclaving was used for sterilisation, but it is not clear why this caused a depression of cell growth on the material in contrast to alcohol sterilisation. The mechanism is not clear but the outcome is of importance to future in vivo implantation.

No evidence was provided or identified by the Inquiry showing large animal pre-clinical studies using POSS PCU as a tracheal implant. To the best of our knowledge, there are no publications or available in vivo studies of POSS PCU tracheas in animals, which would support the use of this material for translation to the clinic.

In conclusion, the Inquiry felt evidence was provided that POSS-PCU can maintain its structural integrity over extended periods and does not degrade or generate toxic leachables. However, there is no evidence that the nanocages at the surface of the POSS-PCU promote epithelial growth or that luminal porosity is adequate to enable cell viability and growth. Although there is evidence that the peripheral pores allow robust tissue ingrowth, there is no evidence of remodelling to create cartilage. Furthermore no evidence about the effects of microbial contamination at the surface was given and that the implant had the mechanical compliance to avoid damage to tracheal remnants. In the opinion of the Inquiry, validation of the methodology of cell and tissue incorporation both in vitro and in a large animal tracheal transplant study, should have taken place before its clinical application.

6.3.3 Other Clinical Applications of POSS-PCU constructs

Two other clinical applications of POSS-PCU were brought to the attention of the Inquiry:

The first relates to research carried out between 2013 and 2014 by Professor Seifalian in collaboration with Mr Ashesh Bhumkar, an ENT surgeon to implant POSS PCU samples into patients in Mumbai, India which was the subject of a Research Misconduct Investigation in March 2015 (reference Section 4.3.21.2).

The Tracheal Transplant Protocol also reports the implantation of a lacrimal duct conduit in a patient, which is reported to have been carried out by Dr Karla Chaloupka in Zurich. At that time the lachrymal duct conduit appeared to have functioned well after months of implantation without occlusion or significant peri-conduit inflammation. UCLB were not aware that a POSS-PCU construct had been administered to this patient until after the procedure had taken place and no MTA was released for this product (Chaloupka et al 2011).

The Inquiry has seen no evidence to suggest that any of these constructs were made in compliance with the Medical Devices Regulations 2002.
6.3.4 BIOtrachea Report

With effect from the end of April 2015 the European Commission terminated the Biotrachea grant. In their letter of 3rd December 2014 the Commission made reference to the Quality Control report from another partner in the Consortium: "POSS 3D tracheal scaffolds: Preliminary Investigation". That report stated that nine samples of the requested tracheal scaffolds received from UCL, had severe and numerous technical deficiencies. These included macroscopic deformities (some samples were remarkably bent and/or collapsed inward on the backside, defects were present along the external surface, the luminal side, discontinuities were found along the inner surface and large variations in thickness were detected). In addition, microscopic defects (round isolated defects, surface irregularities, area of microstructural inhomogeneity) were found in the samples.

In its termination letter of 20th February 2015 the European Commission draws attention to the following scientific conclusion:

"2.3.1.6 Benefits and risk assessment

Based on the so-far clinical experience we cannot pursue on utilizing the POSS-PCU scaffold in its current form. The above-mentioned points (2.3.1.2) are extremely hazardous for the patients’ health and must be therefore further investigated prior continuing any clinical application."

6.4 Recently Published Animal Data

A paper was presented to the Inquiry in July 2017 (Maughan et al 2017), which had been recently accepted for publication. The manuscript investigates different scaffold materials for tracheal replacement in a rabbit model of transplantation. This study compared POSS-PCU, preserved cadaveric homograft (Herberhold) and decellularised tracheal grafts. Scaffolds were implanted into the cervical trachea of 4 rabbits per group without cell seeding. Controls received autotransplanted tracheal segments. Animals were monitored by repeat bronchoscopy for 30 days. All surgical controls survived to termination without airway compromise. In contrast 3 of 4 animals in both the Herberhold and POSS-PCU groups and all of the animals in the decellularised tracheal allograft group required early termination due to respiratory distress. Herberhold grafts showed intense inflammatory reactions anastomotic stenosis and mucus plugging. Synthetic graft integration and vascularisation was poor. Decellularised grafts demonstrated malacia and collapse but had features suggestive of vascular connection or revascularisation. POSS-PCU grafts were uniformly encapsulated in fibrous tissue with little or no integration into surrounding tissues with concentric anastomotic stenosis from granulation tissue.

The article has been accepted for publication by the journal 'Laryngoscope' and will be published later in 2017.

6.5 Conclusions

In conclusion, the POSS-PCU material was a rational design for the generation of new implants specifically tailored for cardiovascular applications. Systematic in vitro and in vivo animal studies were carried out to provide externally validated data which was used for a successful application to the MHRA for clinical trial. However, there is little evidence that supports the translation of this material to the clinic for other regenerative medicine applications. The Inquiry specifically felt that the use of this material for tracheal implants in
patients was not justified and premature due to a lack of supporting *in vitro* and *in vivo* animal data. Although there was significant evidence of an array of biological and polymer materials being used for tracheal research in general, the clinical/scientific team did not provide specific translational data to support the use of POSS-PCU for treatment of patients. It is of particular concern that the POSS-PCU constructs administered clinically as the tracheal construct to the Karolinska Institute for Patient B, the vascular construct implanted into a young man in Tehran, the lacrimal duct construct implanted into a patient in Zurich and the post-auricular discs implanted into patients in Mumbai, were not manufactured to accepted quality standards of GMP meeting the requirements of the Medical Devices Regulations 2002 and were released without the knowledge or consent of UCLB.
Chapter 7: Clinical cases

7.1 Introduction

This chapter documents clinical cases of transplantation of synthetic or bioengineered cadaveric trachea in which employees of UCL have been involved. Many of these cases have been described in the medical literature or are in the public domain. For the purposes of clarity members of the Inquiry are not experts in tracheal transplantation. The Inquiry is aware that there are ongoing academic arguments between experts in airway transplantation concerning the optimal strategy for tracheal replacement. It was considered beyond the scope of the Inquiry to take a position on these arguments and the Inquiry has focused principally on the governance and regulatory approval of cases.

7.2 Patient A

Patient A is the well-reported case of a transplant of a bioengineered cadaveric trachea in a 36-year old woman in Barcelona which took place in June 2008 UCL had no direct link to this case. However, the Inquiry felt that this case was important to consider in a historical context in order to explain how Professor Macchiarini, then an employee of the University of Barcelona, and Professor Birchall, then an employee of the University of Bristol, first cooperated in a clinical context and where the field of tracheal transplantation emerged from.

Professor Macchiarini had been employed by the Barcelona Hospital Clinic as a thoracic surgeon and had been referred a 36-year old Columbian woman who had severe stenosis of her left main bronchus as a consequence of tuberculosis. A clinical decision was made by Professor Macchiarini to treat this woman by using a decellularised human trachea and to seed this with both autologous epithelial cells and mesenchymal stromal cells (MSC). He and Professor Birchall had, at that point, a long-standing research collaboration around animal models of airway transplantation. The animal data which underpinned the use of recellularised tracheas was subsequently published in 2010 and demonstrated that decellularised trachea with chondrocytes and epithelial cells was superior to either alone or neither (Go et al 2010). Professor Macchiarini contacted Professor Birchall in Bristol to ask for his assistance in preparing cells to use in the transplant. At that time Professor Birchall was involved in research which included expanding primary respiratory epithelial cells. His colleague also at the University of Bristol, Professor Anthony Hollander, (now at the University of Liverpool) had developed expertise in differentiating MSC into chondrocytes. The cadaveric trachea was procured and decellularised in Padua, Italy and autologous bronchial epithelial cells and MSC were sent to Bristol for expansion. This cell preparation took place in a newly built veterinary laboratory that was not a licensed Tissue establishment under the Human Tissue (Quality and Safety for Human Application) Regulations 2007. Correspondence from the HTA dated 9th June 2008 relating to the epithelial cells stated that their understanding was that Professor Birchall had established that the samples were not considered to be Medicinal Products or Investigative Medicinal Products, both of which fall under the remit of the MHRA, and confirmed that cell lines fell under their remit. They further indicated that because epithelial cells were being processed and stored in Langford Bristol that a HTA licence was required but that they did not intend to take regulatory action to prevent the use of the cells on the basis that their intended use was for a life saving therapy, and requested further assurance in writing that the processing, labelling, storage and traceability requirements of the Act would be met. The specific
The wording of the letter indicated that the HTA believed that the patient had oesophageal cancer and that the procedure was life saving (she had a benign tuberculous stenosis of her left main bronchus). The Inquiry has ascertained that the HTA received no correspondence from Professor Birchall or any other person involved in the care of Patient A, that indicated that she had life threatening oesophageal cancer. Where this comment in the HTA letter came from is therefore unknown. The Inquiry was not in receipt of any regulatory correspondence in respect to the manufacture of the autologous MSC and chondrocytes. The cells were prepared and shipped to Barcelona and were added to the decellularised cadaveric trachea in Barcelona by Professor Macchiarini and his team. The Inquiry understands that the procedure was approved by the Spanish Transplant Authority and Barcelona ethics commission but are not in receipt of any regulatory correspondence in this regard.

The surgery and the outcomes of this case have been extensively debated and discussed in the scientific and general media. (Macchiarini et al. 2008; Gonfiotti et al 2014). In short Patient A experienced good early airway function but 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.

7.3 Patient B

This patient was the first recipient of a synthetic trachea in June 2011. This patient was a 36-year old Eritrean man living and studying as a postgraduate student in Iceland. This case has been extensively investigated and described in the report of the Karolinska investigations (The Macchiarini Case section 9.1 and Karolinska Institutuet and the Macchiarini Case section 9.1). It was felt unnecessary for the current Inquiry to investigate the clinical outcomes of this case as this was much more appropriately done by the investigatory team appointed by the Karolinska University Hospital. The Inquiry has focused on the events involving UCL researchers leading up to the development of the synthetic trachea and its subsequent transplant.

Patient B was referred to Professor Macchiarini by clinicians in Iceland. At this time Professor Macchiarini had relocated to the Karolinska Institute in Stockholm as a Professor of Thoracic Surgery. He had also been appointed as an honorary Professor at UCL and visited London periodically as part of his research collaborations. Patient B had a slow growing carcinoma of the trachea. Professor Macchiarini made the clinical decision to surgically remove the tumour and to replace the affected segment of trachea with a synthetic graft.

In London in 2009 Professors Birchall and Seifalian had established a basic science research interest in the potential use of the polymer POSS-PCU developed by Professor Seifalian as a material to use in tracheal and laryngeal surgery. As described in Chapter 6 POSS-PCU had been developed for use as a vascular graft and from 2009 onwards there was an interest in Professor Seifalian's laboratory and through its collaborations in exploiting POSS-PCU in other clinical applications. Professors Seifalian and Birchall had a jointly supervised PhD student, Claire Crowley who, from September 2009, was undertaking research into the structure and properties of POSS-PCU in the context of a possible material for use in the airway. Her research looked at changing the physical characteristics of the polymer surface to attempt to facilitate cell adhesion and growth. She had also been studying the structure of the trachea and experimenting using different forms of POSS-PCU to replicate the cartilage rings and membranous components of a trachea. She was principally supervised by
Professor Seifalian and worked in his laboratory but met regularly with Professor Birchall. Professor Macchiarini had been introduced to Professor Seifalian but did not have an active participation in the research programme around POSS-PCU. POSS-PCU biocompatibility had been studied subcutaneously in sheep and as a vascular graft in rats but not at an air interface. Human bronchial epithelial cell attachment was studied in vitro but not in animal studies. There were no animal studies of POSS-PCU tracheal constructs carried out either with or without cellularisation.

In May / June 2011 Professor Macchiarini approached Professor Seifalian directly and asked him if he could manufacture a POSS-PCU tracheal scaffold that could be used for a transplant procedure. Professor Birchall was not involved in this process. CT scan reconstructions of Patient B’s trachea were sent to Professor Seifalian who engaged a glass blower to make glass mandrels to the sizes of the luminal diameters of the CT scans and on this the POSS-PCU trachea was manufactured by Claire Crowley under the instruction of Professor Seifalian. At the time Claire Crowley was in the first year of her PhD studies. It was reported that early tracheas made in this way were examined by Professor Macchiarini and found to be too soft and so the wall of the construct was made thicker. These products were made using research grade - not GMP grade - materials and were manufactured in Professor Seifalian’s research laboratory at the RFH. It is unclear as to whether any Quality Control was carried out apart from mechanical properties. The responsibility for the manufacture lay with Professor Seifalian.

On direct questioning Professor Seifalian confirmed that he did not seek approval or advice regarding the legality or otherwise of manufacturing a clinical grade product or transferring this to Professor Macchiarini for the purpose of transplantation in a human. He did have some awareness of the need for preclinical animal experiments and MHRA involvement through his prior work with Professor Hamilton on POSS-PCU vascular grafts. He said that he made UCLB aware that he had been asked to manufacture a trachea and that he had supplied two tracheas for human use. UCLB testified that they were not aware that a tracheal construct had been released to the Karolinska Institute for clinical application until after the transplant had taken place and that no MTA was released for this product.

In written testimony to the Inquiry Professor Macchiarini indicated that he was not aware that the POSS-PCU tracheal constructs had not been made to GMP. The Inquiry reviewed the Transplant Airway Protocol submitted to the Karolinska Institute ethics committee and found it to be misleading in a number of respects. Specifically the transplant airway protocol included references to the use of undifferentiated stem cells (in fact bone marrow mononuclear cells and biopsies of respiratory epithelium were used to seed the construct), the inference that in vivo animal validation studies had been carried out at GLP/GMP conditions for tracheal application, when in fact the single study referred to related to the GLP validation work on vascular grafts, and references to other clinical applications which relate to unauthorised applications of non-GMP POSS-PCU constructs in patients as a vascular graft and lacrimal duct conduit.

Two tracheas were made and sterilised by autoclaving and then transported to Professor Macchiarini at the Karolinska using a commercial courier. No cellular products were added to the synthetic trachea in London and so, in the opinion of the Inquiry, this product should be classified at this stage as a medical device. Professor Seifalian suggested to Ms Crowley that she should travel to Stockholm to witness the surgery as it might be a valuable
experience for her as a scientist undertaking a PhD in this field. Ms Crowley travelled to Stockholm as an observer since her PhD thesis was centred around the development of POSS-PCU as a potential airway scaffold, but was not involved in the transportation of the tracheas, which had already been sent by commercial courier.

Autologous bone marrow-derived mononuclear cells were added to the POSS-PCU trachea, which had been autoclaved in a facility in Stockholm and it was cultured for 72 hours before the trachea was transplanted. Early reports of the progress of the patient came from Professor Macchiarini and all of the feedback received by Professor Seifalian in London was that the operation had been a tremendous success. In a written statement given to the BBC journalist Fergus Walsh just 4 weeks after the transplant of Patient B, Professor Macchiarini reported to him that neovascularisation of the trachea had been almost instantaneous and that patches of epithelialisation had been evident from day 4 post operatively. No objective evidence was provided to support these claims.

The clinical outcome of the case has been described extensively in the Investigation Reports and this Inquiry will not repeat this component of the investigation. The salient points regarding the POSS-PCU transplant are given below:

- The graft functioned as a conduit for a period of time.
- There was no objective evidence of neovascularisation of the graft.
- There was no objective evidence of epithelialisation of the graft.
- Bronchoscopy evidence demonstrated a biofilm coating the inside of the synthetic graft populated by bacteria and fungi.
- There was no integration between the POSS-PCU scaffold and the native trachea or bronchi either proximally or distally, indeed towards the end of the patient's life there was evidence of detachment. At post-mortem the graft was found to be completely detached from the trachea and bronchi.
- The graft eroded into the oesophagus causing a significant oesophageal fistula which communicated through the detached distal anastomosis to the trachea - a trachea-oesophageal fistula. At post mortem examination a very large defect was evident in the anterior wall of the oesophagus, with the POSS-PCU graft sitting in a pool of liquid.
- The ciliary epithelial escalator function of the trachea was never restored and the patient was prone to multiple respiratory infections.
- Patient B died in 2014.

The Inquiry has seen no evidence that the death of Patient B was reported to the MHRA as a serious adverse incident.

7.4 Patient C

In early 2010 Professor Macchiarini received direct email contact from the mother of a 19-year old female patient with a slow growing cancer of the trachea. Patient C was being treated at Guy's Hospital in London under the supervision of Dr Ricardo Simo an ENT Surgeon. The surgical plan devised by Dr Simo and Dr Karen Harrison-Phipps a thoracic surgeon also working at Guy's and St Thomas's NHS Trust was to resect the tumour which
would also have required removal of the thyroid gland and upper trachea and removal of the laryngeal nerves and oesophagus with the stomach pulled up and the creation of a permanent tracheostomy.

Professor Macchiarini visited the patient and reviewed her records and imaging while he was in London on other business.

On 29th May 2010 Professor Macchiarini received an email from Professor Paul O'Flynn thoracic surgeon at UCLH, copying in Professor Birchall and Professor Paul Stimson (both ENT surgeons at UCLH) asking about possible treatment alternatives to that suggested by Drs Simo and Harrison-Phipps and mentioning the possibility of tracheal transplantation.

Professor Macchiarini provided evidence that he reviewed new imaging of Patient C and wrote that the only curative solution that he could see would be to undertake tracheal transplantation. He further informed the UCLH airway team that he would not consider operating on her at UCLH because he did not have operating privileges but could perform the surgery in Florence at the Careggi Hospital where he held a position.

The basis of the clinical decision was that resection of the tumour would necessarily involve resection of a 360° Segment of the trachea and part of the oesophagus and that this would require a tubular graft replacement in the form of a tracheal transplant.

The Florence ethical committee accepted the clinical protocol and approved the procedure.

Her case was performed in the Careggi Hospital in Florence using a decellularised cadaveric tracheal graft obtained from a donor in Italy under the Italian Transplant Authority. The graft was seeded with autologous cells, but the nature of these cells and whether this was done in a manufacturing unit or theatre is not known to the Inquiry. She also received intraoperative radiotherapy. Both the decellularisation of the trachea and the isolation and seeding of autologous cells was performed in Florence and the team in London associated with UCLH were not involved in this process. Patient C received intraoperative radiotherapy as part of her treatment. Mr O'Flynn travelled to Florence to observe the surgery and asked to be scrubbed at the operating table. Professor Macchiarini provided evidence that the Medical Director of Careggi, Dr Valter Giovanni, granted permission for Mr O'Flynn to be present at the surgery.

The transplant in Florence was funded by the NHS according to Patient C's mother. Professor Macchiarini confirmed that the Careggi Hospital had made a cost estimation for the procedure including intraoperative radiotherapy and aftercare which was estimated to be approximately £60,000. In his evidence, Professor Macchiarini said that he did not derive personal financial benefit from this procedure.

After this transplant Patient C demonstrated improvement in function and was able to return home for a period. Unfortunately, she developed collapse of her trachea which was thought to be related to a graft infection and she required intensive care admission in London for 6 months. At some point Professor O'Flynn performed a tracheostomy through her transplanted trachea. Professor Macchiarini said that he thought that this was not the best management option for her based on the information that he had and that she might have been better served by a stent. She later developed a tracheoesophageal fistula. A number of Multi Disciplinary Team (MDT) meetings were held to discuss how to manage the airway of this patient. Her cancer had recurred and was no longer amenable to surgical resection. In September 2011 a decision was made to try to provide a palliative solution by transplanting
a synthetic trachea made of POSS-PCU. Professor Macchiarini opposed this decision because he believed that there were other therapeutic alternatives. Professor Macchiarini claimed that he was not involved in the decision making process at this time.

The decision to perform a synthetic transplant was informed by the apparent good initial clinical results from Patient B who had received a POSS-PCU trachea in Stockholm 3 months earlier. A colonic interposition graft was also required to replace the oesophagus. A POSS-PCU graft was manufactured at the RFH under the direction of Professor Seifalian. Again there is no evidence that the POSS-PCU trachea was manufactured to GMP. Professor Seifalian denied his involvement under testimony and indicated that the graft had been made by his PhD student under direction from others. The Inquiry were provided with testimony from 3 other witnesses to the effect that Professor Seifalian was involved in the manufacture of this graft either directly or through supervision of his PhD student. The Inquiry found Professor Seifalian's denial of involvement either implausible or, if true, a dereliction of his responsibilities as the expert responsible for developing the product and head of the laboratory.

The POSS-PCU scaffold was transferred to the Centre for Cell, Gene and Tissue Therapeutics unit under a Material Transfer Agreement issued by UCLB. The Centre was aware that the construct had been manufactured in a research lab without approval for the manufacture of implantable medical devices and a risk assessment was carried out by Professor Mark Lowdell, Director of the Centre, his senior management team, and the Chief Pharmacists of both the RFH and UCLH. The Centre carried out a qualification of the construct including assessment of sterility and leachables. The decision to use a scaffold produced in a research laboratory was reviewed by the MHRA and the risk assessment and downstream processing undertaken by the Centre for Cell, Gene and Tissue Therapeutics was acceptable to them. The POSS-PCU construct was seeded with autologous MSCs and epithelial cells in a rotating bioreactor for 48 hours to GMP under the MHRA Specials licence held by Professor Lowdell and transferred to UCLH. The MSC seeding protocol was based on data from Dr Crowley's MSc and early PhD work and the epithelial protocol on advice from Professor Sam Janes. The MSCs were seeded with the idea that they may enhance vascularisation of the graft. A second 'back up' non-cellularised trachea was prepared under the direction of Professor Seifalian and transferred under a separate Materials Transfer Agreement to UCLH.

The composite product was transferred to UCLH with permission from the UCLH Chief Pharmacist to supply the Special to Mr O'Flynn and the Chair of the UCLH Use of Medicines Committee which approved the addition of the Special to the formulary at UCLH. The transplant was performed by Mr O'Flynn and his team and was followed by a prolonged ITU stay. The patient was discharged home for 3 months but then readmitted with symptoms of pneumonia and bleeding. Urgent bronchoscopy was performed by Professor Janes which demonstrated that the graft had separated at the lower end and was detached from the lower trachea/ bronchi leading to an oesophageal fistula and mediastinitis. This was considered a terminal event and the family were informed. She died later the same day.

Professor Lowdell submitted a report via the Pharmacovigilance (Specials) on-line reporting system in line with the policy of the Centre for Cell Gene and Tissue Therapeutics at RFH with regard to products released under their MS authorisation.
7.5 Tracheal Stenosis in Children and Management Options

Tracheal stenosis is a variable condition, which in children is usually congenital. Some patients have short segment stenosis and these are less than 50% of the length of the trachea. The more challenging group to manage are children who have long segment tracheal stenosis. By definition long segment tracheal stenosis describes those patients who have a stenosis that affects more than 50% of the length of the trachea. Typically patients with congenital tracheal stenosis have complete circular rings of cartilage in the trachea instead of 'C' shaped rings of cartilage. A small population of children have complete tracheal obstruction at birth and require extracorporeal membrane oxygenation from birth to survive. The luminal diameter varies but patients referred to the Tracheal and Aerodigestive Service at GOSH typically have a luminal diameter of 1 -2 mm which causes significant restriction of breathing.

Early management focused on the creation of a vertical slit in the stenotic portion of the trachea and the insertion of a patch made of cartilage, pericardium or some other suitable material to increase the internal luminal diameter of the trachea. Two types of patch have been used. The first is the heterograft which might be made of bovine pericardium or a synthetic material such as Goretex. The long term success of these heterografts is reportedly poor and they have largely ceased being used. The other type of patch is the homograft which is effectively a formalin fixed cadaveric human trachea (Herberhold technique). In both cases the surgery involves sewing the patch into the trachea to increase the luminal diameter. Healing of either type of graft is associated with shrinkage and reduction in luminal diameter and so it is usual to make the graft larger than would seem to be needed. Due to the relatively soft nature of the hetero or homo graft mechanical collapse is not uncommon and has required the use of radial balloon dilatation or stenting. It has been practice to insert a metal stent that can be serially dilated as the child grows and in this situation the stent becomes embedded in the wall of the graft and both are covered with epithelium between 3 and 6 months after insertion. However, this approach is not without problems, the most concerning problems being migration of the stent through the relatively thin tissue of the graft and erosion into nearby vascular structures causing bleeding. Modern polydioxanone sulphate (PDS) absorbable stents have less risk of vascular erosion.

A new procedure replaced the use of heterografts and homografts for tracheal stenosis which was called slide tracheoplasty. This procedure involves dividing the trachea and creating a vertical slit in the posterior aspect of the upper end and the anterior aspect of the lower end and then sliding one over the other and suturing them together. This movement of one end over the other creates a wider lumen but shorter trachea and has been demonstrated to have good clinical outcomes in children. It is not suitable for all children however and particularly those with long segment tracheal stenosis can often not be treated in this way. In those that can be treated the trachea grows relatively normally thereafter.

Most children presenting with congenital tracheal stenosis require surgery within the first year of life and many within 6 months after birth. Many children will require more than one surgical procedure during their lifetime. Congenital tracheal stenosis may also be associated with developmental anomalies of the heart or great vessels which may require correction at the same time as the trachea.
7.6 Patient D

This 12-year old boy presented with long segment tracheal stenosis at birth. As a baby he had been treated with extracorporeal membrane oxygenation and had sustained a diffuse cerebral injury related to this ECMO treatment. He had some limitation in mobility as a consequence of this. His first procedure was a vertical tracheoplasty with the defect closed using a pericardial patch. He required an endotracheal stent within 3 months of the surgery and underwent subsequent dilatation of the stent. His metal stent eroded into his innominate artery and was removed at the age of 3 years and his vessel repaired. This time his tracheal defect was repaired using a homograft using the Herberhold technique, which involves preservation of the posterior wall of the trachea and replacement of the anterior component with a cadaveric tracheal homograft preserved using formaldehyde. This type of homograft typically shrinks with scarring after a period of months and so it is necessary for the surgeons to suture in a homograft which is larger than appears necessary. His trachea including the homograft became fully epithelialized. This homograft lasted until he was 10 years of age but did require the insertion of a metal stent to maintain the luminal airway. In 2009 this stent again eroded into a major blood vessel this time the aortic arch. In addition to bleeding he also had recurrent tracheal stenosis extending over most of the trachea, a measured length of 7cm. He was referred again to GOSH. A further homograft was the first consideration however, it was considered extremely unlikely that there would be a strip of native trachea that could be preserved on the posterior aspect of the trachea on which to suture the Herberhold homograft and the team considered that a complete tubular replacement was required. His case was discussed at several MDT meetings at GOSH and by telemedicine with the intensive care unit in the remote hospital where Patient D was located. At these meetings there were representatives from thoracic surgery, cardiology respiratory medicine, ENT, play therapists and psychologists. His case was also discussed regularly with his family by telemedicine and was reviewed by the CES team at GOSH. The recurrent bleeding secondary to stent erosion made resolution of this problem a clinically urgent situation. Given the extent of his previous surgery, the length of his stenosis and the unavailability of further homograft material a decision was made to remove the stent and remaining homograft and perform a decellularised cadaveric tracheal transplant repopulated with autologous cells. It is important to note that this was a clinical decision made by an NHS multidisciplinary team on compassionate grounds.

In March 2010, the clinical intervention was led by Professor Martin Elliott who also took the responsibility for the surgical preparation and plan. Professor Macchiarini was in London at that time and was invited to be involved since at that time he was the only person worldwide who had undertaken a decellularised tracheal transplant (Patient A). There was some disagreement about how to conduct the procedure as Professor Macchiarini favoured an unstented graft but Martin Elliott insisted that the graft was mounted on a PDS absorbable stent. The reason given for Professor Elliott's decision was because of his experience with preserved homografts which he described as undergoing a period where the graft becomes very soft shortly after transplantation and before vascularisation occurs.

The tracheal graft was procured in Florence, Italy under the Italian Transplant Authority approval and was decellularised using a protocol that had been used previously with vacuum-assisted decellularisation. The trachea was seeded in theatre with bone marrow mononuclear cells and tracheal epithelial explants (Elliott et al 2012; Hamilton et al. 2015).
The surgical protocol varied from that of previous patients in that a vascularised pedicle of omentum was brought up from the abdomen and wrapped around the graft with the hope that this might provide a source of vascularisation for the graft.

The clinical outcome was initially good with evidence of vascularisation within 12 weeks and epithelialisation at 4-6 months. The patient required numerous procedures to clear secretions and granulation tissue. The graft became malacic and required several stents and ITU admissions within the first year, but the patient was alive and at school after 6 months. He has required one further intervention in 2013 but is at school and has shown evidence of growth and development.

7.7 Patient E

Patient E was a 15-year old girl who 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.

Her case was discussed in the NHS services at GOSH at several MDT meetings and also by the CES. The key aspects of her case was that almost the whole length of her trachea was affected. She was considered unsuitable for a Herberhold homograft transplant and it was decided to offer a decellularised tracheal transplant repopulated with autologous bone marrow derived MSC and respiratory epithelial cells.

The trachea was procured under the RFH HTA licence and decellularised using a vacuum technique. It was recellularised with autologous MSCs and epithelial cells at the Centre for Cell, Gene and Tissue Therapeutics at GMP under their MHRA Specials licence using xeno and allo free reagents.

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. When the native trachea was removed there was no viable posterior wall of trachea confirming that the Herberhold technique would not have been an appropriate approach and that a tubular tracheal replacement was required.

Professor Elliott, described how, because there had been an attempt to epithelialise the graft, he was advised not to place an absorbable stent at the time of tracheal transplant. His preference was to have placed a stent because he had previously observed a phenomenon with Herberhold homografts where the graft became soft and supple in the weeks after transplant before becoming biomechanically more rigid later in its life history.

Following surgery the patient was rapidly extubated and was up and out of bed within 48 hours. She was described as having never been better from a breathing perspective. Over
the next few days her recovery continued to improve. There was pressure on GOSH from further patients with complex long segment tracheal stenosis awaiting admission and as a consequence of this the tracheal team felt pressure to discharge the patient to the care of the local regional airways team who were described as "well able" to deal with airway issues. 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. When asked her family were grateful for the opportunity that her daughter received and held no rancour with the tracheal team at GOSH

Professor Elliott offered that the team felt that there were valuable lessons to be learned from the case of Patient E and criticised the system of medical literature publishing for its insistence on only publishing positive results. He described how it had taken the team a protracted period of time to find a journal that would publish the adverse outcome of Patient E (Elliott et al 2017). He proffered an alternative system with an honest broker collecting data prospectively from all patients undergoing novel procedures for whom ethical approval has been obtained. He commented further that no surgeon and no patient (or their family in the case of children) should be allowed to perform or undergo such novel procedures unless they agree to share their data. Professor Elliott has now retired from clinical practice and has undertaken to try to establish such a registry of novel and complex cases.

7.8 Patient F

Patient F is a 3-year old girl with severe airway malacia secondary to multiple repaired tracheoesophageal fistulation. She had swallowed a lithium battery at the age of one, which had become lodged in her oesophagus and eroded over a 2.5cm length into her trachea. She had been transferred to GOSH and underwent a slide tracheoplasty, oesophageal repair and a laparoscopic gastrostomy. She required multiple oesophageal dilatations and also required tracheal stenting for tracheomalacia. She has had 27 oesophageal or tracheal dilatations and has required 3 endotracheal stents. She had to have a cervical oesophagostomy and resection of her mid oesophagus because of recurrent fistulation into the trachea. She has developed problems with granulation in the lumen of her shortened trachea. Further surgical procedures were felt unlikely to be successful in view of her previous extensive tracheal surgery and tracheal shortening. Homograft was considered but was thought unlikely to be possible. Her case was discussed at multiple MDT meetings and with clinicians in her home town and also with her parents. Application was made to the Clinical Ethics Service team at GOSH who offered no ethical objection to the use of tracheal transplantation.

She underwent a cadaveric tracheal transplant in May 2017. The graft was obtained through the NHS Blood and Transplant under the Royal Free HTA licence and decellularised using a vacuum technique. It was recellularised with autologous bone marrow-derived MSCs and epithelial cells at the Centre for Cell, Gene and Tissue Therapeutics at GMP under their MHRA Specials licence using xeno and allo free reagents. The precise details of the surgery
are unknown but it was proposed to deploy an internal biodegradable stent at the time of transplant and to use an omental wrap if this were possible. The patient is under the care of Mr Richard Hewitt Director of the Tracheal Service at GOSH. Early reports were that 2 months after her surgery Patient F was recovering well but no further details of her condition have been reported. The Tracheal Service have undertaken to formally report the outcome of Patient F in the medical literature in due course.

7.9 RegenVox

RegenVox is a Phase I/IIa clinical trial of stem cell based tissue engineered partial laryngeal implants in 10 adult patients with end-stage laryngotraheal stenosis with 24 months follow up. The trial involves the implantation of an allogeneic decellularised partial larynx reseeded with autologous bone marrow mesenchymal stromal cells. Preclinical studies in 16 pigs with seeded laryngeal implants are reported as demonstrating 81% survival at 2 months and that the decellularised scaffolds showed mild inflammatory responses and evidence of remodelled cartilage. In a subsequent six-months' survival study in 8 pigs, a two-stage implantation procedure was used with improved anatomical reconstitution of the vocal cords. One animal died of an unrelated ear infection, but the remaining seven were healthy, eating and vocalising normally until euthanised.

The donated larynx will be supplied by NHS Blood and Transplant (NHSBT) under their HTA licence and will be decellularised by the Centre for Cell, Gene and Tissue Therapeutics at the Royal Free Hospital. The autologous MSCs will be expanded at the Centre for Cell, Gene and Tissue Therapeutics and seeded into the scaffold in a bioreactor at GMP. The resultant primary ATIMP will be implanted in a muscle or fascio-cutaneous flap to allow vascularisation. At 7-11 weeks the graft will be relocated to its orthopic position and a split thickness skin graft will be used to facilitate early epithelialisation. The Principal Investigator is Professor Birchall, UCL is the sponsor, and 4 hospitals are involved: UCLH, RFH, Charing Cross Hospital and Queen Elizabeth Hospital Birmingham. The study received ethics approval from the Health Research Authority in July 2014 and a Clinical Trial Authorisation from the MHRA in February 2015.

7.10 Inspire

Inspire is a Phase I open-label study to assess the safety, tolerability and potential efficacy of a novel tracheal replacement consisting of a tissue engineered decellularised tracheal scaffold with seeded autologous mesenchymal stromal cells in subjects with severe tracheal stenosis or malacia. Following surgical implantation, the trial product will be supported by a series of stents (including Glyaderm®). Four adults will be recruited to the study. The Principal Investigator is Professor Birchall and the sponsor is the Cell and Gene Therapy Catapult. The trial received Clinical Trials Authorisation from the MHRA in October 2015 and a favourable ethics approval from the Health Research Authority in January 2016.

7.11 Conclusions

The Inquiry makes no further commentary on Patient A since UCL was not involved.

The Inquiry makes no comment on the clinical condition and management of Patient B since this has been the subject of scrutiny by the Karolinska Institute. However, the Inquiry is concerned that the POSS-PCU construct used in Patient B had not been subject to appropriate pre-clinical studies in a tracheal context and was not manufactured to GMP
under the relevant UK legislation and licensure. Moreover the Inquiry found the information presented to the Karolinska Institute was misleading in a number of regards. It is not possible for the Inquiry to judge whether the Karolinska would have taken the same or a different view in respect of the clinical intervention in Patient B had they been in possession of a more accurate representation of the facts.

In respect of Patients C (second transplant), D, E and F, the Inquiry recognises the serious challenges faced by clinical teams in having to decide how to manage rare life threatening situations, often in children or young adults when there may be little precedence on which to base decisions. These compassionate procedures were carried out after full debate as to the therapeutic options by a multi-disciplinary team and in accordance with established organisational approval procedures. The products for Patients C, E and F were manufactured by the Centre for Cell, Gene and Tissue Therapeutics to GMP under the relevant legislation and licensure.

The Inquiry concurs with Professor Elliott that there is difficulty in publishing data where the outcomes are negative, but that this is just as important as positive data in informing benefit-risk decisions and future research and development of the field. We agree that some form of patient registry of compassionate use cases would be of benefit.

Finally, the Inquiry believes that whilst occasional compassionate use is unavoidable, the development of the field is contingent upon rigorous scientific evidence, good manufacturing practices, robust non-clinical evaluation and properly structured clinical trials. The Inquiry has seen evidence that both RegenVox and Inspire studies have received Clinical Trials Authorisation from the MHRA and approval from the independent ethics committee. The Inquiry is mindful of the concerns expressed by some witnesses as to the efficacy and safety of these tissue-engineering approaches, but believes that the best way to resolve such genuine differences of opinion is through systematic preclinical and clinical studies, which have been subject to independent scrutiny by Regulatory Authorities and Independent Ethics Committees. These are the data that will inform evidence-based decisions on the potential benefits and risks of this new generation of Regenerative Medicines in the longer term.
Chapter 8: Recommendations

8.1 Introduction

UCL is one of the leading Universities in the world. Together with its partners it provides international level medical research, contributing to the development of new medicines not just for its local population, but also to the benefit of patients across the UK and the world. The field of Regenerative Medicine holds great promise for the future treatment of many of the degenerative and neoplastic diseases which are of increasing prevalence across most developed economies due to an ageing demography, lifestyle choices and health inequalities. These disorders not only give rise to significant morbidity and premature mortality for individuals, they also generate significant burdens on families, healthcare providers and social systems. The development of Regenerative Medicines is therefore a healthcare, social and economic imperative.

The translation of academic science, through preclinical evaluation, manufacture and clinical trial, and eventually to routine clinical application is long, difficult and arduous and requires multidisciplinary teams capable of working across academia, industry and healthcare. UCLP, and similar organisational clusters elsewhere in the UK and internationally, provide the key infrastructure and critical mass needed to realise the ambition and promise of the field. However, large, complex, multidisciplinary organisational clusters can be challenging to manage and govern. It is not possible for any one individual to have visibility over and understand the full range of activities in such an organisational structure. In addition there are multiple pressures on the organisation and the individuals within it including the desire to offer patients new and effective treatments as soon as possible, the imperative to produce high value publications and attract research funding, and the requirement to contribute towards commercial development of promising research products. These real and legitimate pressures need to be counterbalanced by organisational governance mechanisms, which strike a balance between early access to new therapies for patients who are sometimes in desperate need whilst at the same time protecting them from premature or ill-advised intervention. The very nature of experimental therapies engenders genuine uncertainty as to potential positive and negative outcomes, and not all such judgements will turn out to be successful. However, the organisational governance systems need to facilitate transparency, learning and the confidence of patients, staff and the general public.

The Inquiry saw many examples of excellent science, manufacturing and clinical practice and wishes to commend UCL senior management for its transparency in commissioning an independent Inquiry and also the many individuals who gave freely of their time and expertise, helping us to understand the complex information with which we were presented.
8.2 Recommendations

The Inquiry makes the following recommendations cross-referenced to the evidence where appropriate in the hope that these will help improve governance systems not just within UCLP but also similar organisational clusters elsewhere, and therefore facilitate the development of the field in the UK and internationally:

I. That a unified system of governance for Regenerative Medicine should be introduced across UCLPartners to simplify and standardise oversight and approval processes for all products destined for clinical applications including cell therapy, gene therapy and tissue engineered products, small molecules and medical devices / combinatorial products and across all organisational and geographic boundaries. That the scope of the meta-governance system should include ethics, professional review and quality and regulatory compliance and also connect to issues of research or fiscal misconduct where they might impact upon development of a clinical product (Chapter 3).

II. Clinical academics working in regenerative medicine are often approached directly by patients seeking treatment, frequently in circumstances where all conventional treatment options have been exhausted. Such patients are potentially interacting with researchers at an uncertain interface between academic research and clinical medicine. Creating a pathway for registration and evaluation of these patients may provide a clearer mechanism to signpost patients towards clinical trials or compassionate use routes while also providing the reassurance of a defined process subject to governance for the researcher (Chapter 3).

III. That the process employed to consider compassionate or exceptional use treatments employed at GOSH should form the basis for a single unified model employed across UCLP (Chapter 4).

IV. That whilst the current system for research misconduct investigations is robust, attention should be given to the timely progression and completion of such investigations, and that the possibility of at least one external member being appointed to Screening Panels in serious and/or high profile cases should be considered (Chapter 4).

V. That where it is found necessary to suspend a member of staff or pause a study, timely and confidential communication should be provided to funders and other stakeholders including the likely timeframe for resolution and interim arrangements (Chapter 4).

VI. That UCL should resolve the investigation into the use of vascular POSS-PCU grafts to enable a clear position to be taken on the previously funded research programme "A clinical study to assess the safety and efficacy of POSS-PCU small diameter grafts in arteriovenous access and coronary artery bypass graft (CABG) surgery". The Inquiry considered that unless there is evidence of research misconduct, which would undermine the integrity of the
data submitted to MHRA, that this trial should be supported to proceed (Chapter 4).

VII. That the system for awarding honorary contracts with the University be strengthened through the use of external referees, consideration of the potential risks as well as benefits of the appointment, and the establishment of specific terms of engagement within the honorary contract (Chapter 5).

VIII. That the prima facie evidence that Professor Seifalian's research laboratory did not meet the requirements of the Medical Devices Regulations 2002 (including the exceptional use requirements) during the manufacture of POSS-PCU constructs intended for direct clinical use as tracheal, vascular, lachrymal duct and post-auricular implants (whether as medical devices or combination advanced therapy medicinal products) be reported to the MHRA for further investigation as soon as possible (Chapters 4 and 6).

IX. That UCL should advise the Karolinska Institute that the POSS-PCU construct made for Patient B had not undergone rigorous pre-clinical assessment and was not made to GMP standards under the relevant UK legislation and licensure (Chapter 7).

X. The Inquiry considered that as a general principle, all individuals involved in the manufacture, administration or implantation of biomedical devices for clinical use have a responsibility to be acquainted and compliant with extant regulations that cover their field of work (Chapter 7).

XI. The UCL should take further steps to ensure that students are not put in a position where they are asked to carry out inappropriate activities such as manufacturing constructs for clinical application or giving clinical advice outwith their competencies. UCL should ensure that robust confidential whistle blowing provisions are in place to support students who have concerns (Chapter 7).

XII. That UCL work with other stakeholders both across the UK and internationally to facilitate the development of unbiased patient registries of compassionate therapeutic interventions (Chapter 7).

XIII. That UCL and other stakeholders continue to facilitate properly evidenced and structured clinical trials of novel products to inform and evaluate the development and eventual adoption of the next generation of Regenerative Medicines (Chapter 7).
Chapter 9: References

9.1 Karolinska Institute Investigations


9.2 General References


9.3 Clinical Cases

Patient A


Patient B


Patient D


Patient E

Appendices

Appendix 1
The Inquiry Team

Members of the Inquiry
Chair – Professor Stephen Wigmore (Professor of Transplantation Surgery, University of Edinburgh)
Professor Alicia El-Haj (Professor of Cell Engineering, Keele University)
Professor David Tosh (Professor of Stem Cell & Regenerative Biology, University of Bath)
Professor Marc Turner (Professor Cellular Therapy, University of Edinburgh and Medical Director, Scottish National Blood Transfusion Service)
Professor Pankaj Vadgama (Professor and Director of IRC in Biomedical Materias)

Secretary to the Inquiry
Dr Edward Payne

Legal Advice
Mr Laurence Ward
Appendix 2
Witnesses Who Gave Oral Evidence

Professor Alan Thompson
Dr Alyson Fox
Professor Alexander Seifalian
Professor Claudio Stern
Professor David Lomas
Professor Emma Morris
Professor George Hamilton
Dr Karen Sergiou
Dr Leonid Schneider
Professor Martin Birchall
Professor Tarek Yousry
Dr Catriona Crombie
Dr Claire Crowley
Professor Martin Elliott
Professor Mark Lowdell
Professor Pierre Delaere
Professor Sam Janes
Professor Tony Mundy
Professor Vivek Mudera
Appendix 3
Witnesses Who Gave Written Evidence

Professor Alex Seifalian
Dr Anne Lane
Professor Anthony Hollander
Professor David McAlpine
Ms Edna Murphy
Professor George Hamilton
Dr Jacqueline Barry
Dr Jane Kinghorn
Professor Mark Emberton
Professor Mark Lowdell
Professor Martin Birchall
Dr Michelle Griffin
Professor Paul O'Flynn
Professor Paolo Macchiarini
Dr Joe Brierley
Bosse Lindquist
Matthias Corbascio
Thomas Fux
Karl-Henrik Grinnemo
Oscar Simonson
Appendix 4
Organisations Providing Documentary Evidence

UCL Business (UCLB)
Cell and Gene Therapy Catapult
Human Tissue Authority (HTA)
Karolinska Institute
Medical Research Council (MRC)
The Wellcome Trust
Videregen
Appendix 5  
Acronyms and Glossary of Terms

| Advanced Therapy Medicinal Products or ATMP | An advanced therapy medicinal product means any of the following medicinal products for human use:  
|                                           | • Somatic cell therapy medicinal products (as defined in Part IV of Annex 1 of Directive 2001/83/EC Eudralex, the Rules Governing Medicinal Products in the European Union)  
|                                           | • Tissue engineered products (as defined in Article 2(1)(b) of the Advanced Therapy Medicinal Product Regulation (EC) No. 1394/2007).  
| A Combined ATMP (described below) is a type of ATMP | |
| Artificial Scaffolds | Synthetic material or structure for implantation in medical use designed to encourage cellular ingrowth |
| Cell Therapy | Treatment in which cellular material is administered to a patient |
| Clinical Trials | Study of a novel intervention involving human subjects |
| Combined ATMP | A combined advanced therapy medicinal product means an advanced therapy medicinal product that fulfils the following conditions:  
|                                           | • it must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC; and  
|                                           | • its cellular or tissue part must contain viable cells or tissues; or  
|                                           | • its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to. |
| Decellularised | Manufacturing process for tissues designed to remove the cellular component of the tissue leaving a scaffold which is theoretically non-immunogenic |
| Epithelialisation | Growth of epithelial cells on a surface to form a cell layer |
| Gene therapy medicinal product | Gene therapy medicinal product means a biological medicinal product which has the following characteristics:  
|                                           | (a) it contains an active substance which contains or consists of a |
recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, adding or deleting a genetic sequence;
(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.

<table>
<thead>
<tr>
<th>Good Laboratory Practice or GLP</th>
<th>Good laboratory practice (GLP) is a set of principles intended to assure the quality and integrity of non-clinical laboratory studies that are intended to support research or marketing permits for products regulated by government agencies.</th>
</tr>
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<tbody>
<tr>
<td>Good Manufacturing Practice or GMP</td>
<td>Good manufacturing practices (GMP) are the practices required in order to conform to the guidelines recommended by agencies that control authorisation and licensing for manufacture and sale of food, drug products, and active pharmaceutical products.</td>
</tr>
<tr>
<td>Great Ormond Street Hospital or GOSH</td>
<td>Special Health Board providing healthcare to children including many National Services, part of UCL Partners.</td>
</tr>
<tr>
<td>Health Research Authority or HRA</td>
<td>The Health Research Authority (HRA) protects and promotes the interests of patients and the public in health research.</td>
</tr>
<tr>
<td>Human Tissue Authority or HTA</td>
<td>Public body which regulates the removal, storage, use and disposal of human bodies, organs and tissues for a number of scheduled purposes including transplantation, research, education and training.</td>
</tr>
<tr>
<td>In vitro</td>
<td>Literally translated as 'in glass' term used to designate experiments out of a normal biological environment.</td>
</tr>
<tr>
<td>In vivo</td>
<td>Term used to designate experiments performed within an animal or human.</td>
</tr>
<tr>
<td>INSPIRE</td>
<td>Clinical trial for replacement tracheal technology led by a consortium including Videregen, Cell and Gene Therapy Catapult, University College London (UCL), NHS Blood and Transplant in Speke and the Royal Free London NHS Foundation Trust.</td>
</tr>
<tr>
<td>Karolinska Institute</td>
<td>One of the largest and most prestigious medical universities in the world. Located in Solna within the Stockholm region of Sweden. The Nobel Assembly at the Karolinska Institute awards the Nobel Prize in Physiology or Medicine.</td>
</tr>
<tr>
<td><strong>Laryngectomy</strong></td>
<td>Surgical removal of the larynx</td>
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<tr>
<td><strong>Medicines and Healthcare products Regulatory Agency (MHRA)</strong></td>
<td>Executive agency of the UK Department of Health responsible for ensuring the standards and safety of medicines and medical devices</td>
</tr>
<tr>
<td><strong>MSC</strong></td>
<td>Mesenchymal stromal cells also called Mesenchymal stem cells. Multipotential connective tissue cells with the potential to differentiate into cells with the morphology of cells found in tissues such as bone, cartilage, fat or fibrous tissue.</td>
</tr>
<tr>
<td><strong>National Health Service (NHS)</strong></td>
<td>Publically funded health system providing care to patients in England and other parts of the UK</td>
</tr>
<tr>
<td><strong>Patent</strong></td>
<td>A patent is a set of exclusive rights granted by a state to an inventor to make, use and sell an invention for a limited period of time in exchange for detailed public disclosure of an invention</td>
</tr>
<tr>
<td><strong>Polyurethanes</strong></td>
<td>Polyurethane (PUR and PU) is a polymer composed of organic units joined by carbamate (urethane) links. Different polyurethanes have different properties and can be solid as in flexible plastics or softer as in low density foams</td>
</tr>
<tr>
<td><strong>POSS-PCU</strong></td>
<td>POSS-PCU refers to a composite molecule Polyhedral oligomeric silsesquioxane poly(carbonate-urea) urethane. This molecule combines compliant polyurethane (PCU) with siloxane polyhedral nano cages. This material was developed for use in medical devices</td>
</tr>
<tr>
<td><strong>Regenerative Medicine</strong></td>
<td>Branch of medicine involved in the process of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal function</td>
</tr>
<tr>
<td><strong>RegenVOX</strong></td>
<td>The Phase 1/2 clinical trial, entitled RegenVOX, is funded by the Medical Research Council and is looking at the use of stem cell-based tissue engineered laryngeal implants for certain airway disorders.</td>
</tr>
<tr>
<td><strong>Research Misconduct</strong></td>
<td>Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.</td>
</tr>
<tr>
<td><strong>Somatic cell therapy medicinal product</strong></td>
<td>Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics: (a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use</td>
</tr>
</tbody>
</table>
have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor; and (b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No1394/2007, in particular, shall not be considered as substantial manipulations

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>Narrowing usually related to a tube</th>
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<tr>
<td>The Wellcome Trust</td>
<td>Major UK-based biomedical research funding charity (registered charity number 210183)</td>
</tr>
<tr>
<td>Thoracic</td>
<td>Anatomical term meaning the chest</td>
</tr>
</tbody>
</table>
| Tissue engineered product | A tissue engineered product means a product that:  
  • contains or consists of engineered cells or tissues, and  
  • is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.  

A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, biomolecules, biomaterials, chemical substances, scaffolds or matrices.  

Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions:

  • the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved.  
  • the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor (homologous use).

<p>| Trachea         | Principal airway connecting the larynx to the main bronchi and thereafter the lungs. Known colloquially as the windpipe. |
| Vascularisation | Development of a vascular network or ingrowth of blood vessels |
| University College London (UCL) | Public research University and oldest constituent of the federated University of London |</p>
<table>
<thead>
<tr>
<th><strong>UCL Business or UCLB</strong></th>
<th>UCL Business PLC a public company incorporated in England and Wales with registered number 02776963 and having its registered office at The Network Building, 97 Tottenham Court Road, London, United Kingdom, W1T 4TP</th>
</tr>
</thead>
</table>
| **UCLH**                 | University College London Hospitals NHS Foundation Trust comprises the following hospitals:  
  • University College Hospital Site hospitals  
  • Royal National Throat, Nose and Ear Hospital  
  • Royal London Hospital for Integrated Medicine  
  • National Hospital for Neurology and Neurosurgery  
  • Eastman Dental Hospital |
| **UCLPartners**          | UCLPartners Ltd a private limited company registered in England and Wales with registered number 06878225 and registered office at 170 Tottenham Court Road, London, W1T 7HA                                                                                                                                 |
