Medical Research Council
2nd Floor David Phillips Building, Polaris House, North Star Avenue, Swindon,
United Kingdom SN2 1ET
Telephone +44 (0) 1793 416200
Web http://www.mrc.ac.uk/

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Biomedical Catalyst: DPFS/DCS Full PROPOSAL

Document Status: With Owner
MRC Reference:

Biomedical Catalyst: DPFS/DCS Full Nov 2012
Developmental Pathway Funding DPFS

Organisation where the Grant would be held

Organisation	University College London	Research Organisation Reference:	37396
Division or Department	Ear Institute		

Project Title [up to 150 chars]

RegenVOX: phase I/II clinical trial of stem cell based tissue engineered laryngeal implants

Start Date and Duration

a. Proposed start date	01 April 2013	b. Duration of the grant (months)	50

Applicants

Role	Name	Organisation	Division or Department	How many hours a week will the investigator work on the project?
Principal Investigator	Professor Martin Birchall	University College London	Ear Institute	7.5
Co-Investigator	Professor Anne GM Schilder	University College London	Ear Institute	1.88
Co-Investigator	Professor Alexander Seifalian	University College London	Medicine	1.72
Co-Investigator	Dr Mark Lowdell	University College London	Haematology	1.72
Co-Investigator	Dr Sam Janes	University College London	Medicine	2.31
Co-Investigator	Professor Anthony Hollander	University of Bristol	Cellular and Molecular Medicine	1.87
Co-Investigator	Dr Gareth Ambler	University College London	Statistical Science	2.06
Co-Investigator	Professor Christopher Mason	University College London	Biochemical Engineering	1
Co-Investigator	Dr Tahera Ansari	Northwick Park Institute for Medical Res	Organ Regeneration and Transplantation	3.03
Co-Investigator	Mrs Susan Tebbs	University College London	SLMS Research Support Centre	3.75
Co-Investigator	Mr Gurpreet Sandhu	University College London	Medicine	3.75

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Objectives

List the main objectives of the proposed research in order of priority

The primary aim of this study is the timely delivery of a Phase I/II (safety and early indicator of efficacy) clinical trial of stem-cell based, tissue-engineered laryngeal implants in patients with severe irreversible structural disorders of the larynx unresponsive to conventional treatment.

Deliverables, in order of priority, will be:

1. Safety and efficacy data in a phase I/II trial in ten patients with irreversible severe laryngeal stenosis/malacia;
2. Refined GMP production processes and standard operating procedures for a tissue-engineered partial laryngeal replacement implant;
3. New pathways for reverse translation involving complex stem cell product trials;
4. Economic and business modelling of manufacture and clinical delivery of complex regenerative products developed for orphan indications.

Specific objectives will be:

Months 1-12, Optimisation of recruitment strategies, preparation of final trial documentation, PSF; final testing of production process, QC/RC, bioreactor construction; REC/R&D/CTA approvals
Months 13-20, Recruitment, Intervention, Monitoring
Months 21-44, Follow-up, Continuous improvement of production processes; Use of tissue/blood data by discovery science partners to develop and test hypotheses on behaviour of human stem cells and scaffolds in vivo in man.
Months 45-50, Analysis, Reporting, commercialisation and/or phase III trial plans; reverse translational grant applications.

Summary

Describe the proposed research in simple terms in a way that could be publicised to a general audience.

The larynx protects the airway during swallowing, regulates breathing, and permits voice: all fundamental human functions. Over 2000 UK patients lose laryngeal function due to trauma or cancer annually and need to spend a lot of time at or in hospitals. 1300 NHS patients a year have their larynx removed entirely. Conventional treatments for these patients leave many with substantial problems talking, swallowing and breathing. For example, the use of combined chemotherapy and radiotherapy for laryngeal cancer results in hoarseness and painful swallowing and can even render the larynx completely disabled. However, if we could accurately replace the normal contours and structure of the larynx, for example by using a living tissue-engineered replacement, the quality of life (and in some cases survival) of these patients would be transformed. In this project we build on some well-publicised successes in replacing the windpipes of adults and children to deliver a laryngeal reconstruction product made from the patient's own stem cells and a laryngeal scaffold prepared, with appropriate permissions, from transplant donors. Our goal is thereby to produce a safe, effective and reasonably therapy suitable for routine NHS use, resulting in improved quality of life for patients and carers.

The product will be a partial laryngeal replacement construct, composed of a a human donor scaffold from which all donor cells have been chemically stripped. This means that the implant will not get rejected, like normal transplants, and so patients do not need immunosuppressant medication, with all the side effects that would entail. Based on extensive laboratory work, we are able to turn the patient's stem cells into cartilage-producing cells to give natural strength to the product, and also produce a replacement mucous membrane to line the inside, just like a normal larynx. Similar technology worked well for our adult and child windpipe recipients treated for life-saving reasons. To perform this work, we need a further years' preparation for a clinical trial, which will then follow ten implanted patients for two years in order to demonstrate to the regulatory authorities that the product is both safe and effective. This will, in turn, allow us to apply to use the technology routinely in the NHS and to market it to bring in much needed funds to our hospitals. Since this is the first stem-cell based organ replacement to enter clinical trials to our knowledge, this project has far-reaching 'path-finding' implications for other related organ replacements such as those for oesophagus and lung. Even more value will be

obtained from this work by developing ways of studying cells and tissues in man in trials like this so that we can learn as much about the underlying science of stem cells and tissue repair as possible. Finally, we will study the detailed economics of moving treatments like this into routine healthcare, and determine the most cost-effective ways this can be managed, as well as making sure that any new inventions bring in as much finance as possible to the UK.

Technical Summary

There are no satisfactory conventional solutions for patients with end-stage laryngeal stenosis, which can result from trauma or after cancer resection. This has profound impacts on quality of life, especially swallowing, breathing and talking. Based on our 'first-in-human' successes with tracheal implants1,2, we developed an autologous stem cell and biologic scaffold based partial laryngeal implant to correct severe structural disorders. In preclinical studies, this was biocompatible in rats, and safe and effective in pigs (human cells in immunosuppressed animals). We have developed robust processes for production of cells, scaffold, bioreactor and implant within our fully Good Manufacturing Practice (GMP) licensed cell therapy facility. UCLH hosts the national airway service, which has the largest pool of potential recipients in Europe, and skilled clinical staff.

We propose a 50 months' project to encompass a phase I/IIa clinical trial of customized stem cell based laryngeal implants in ten patients with severe laryngeal stenosis who have exhausted conventional therapeutic options, and with two years' follow-up.

Milestones will be:

1. Obtain necessary authorisations, and perform first implant
2. Complete recruitment and submit processes for IP assessment
3. First two patients attain 6- and 12-month efficacy targets; cost-reduction achieved
4. Completion of follow-up, reporting to MRC and MHRA and publication in high impact journal

Academic Beneficiaries

Describe who will benefit from the research

To our knowledge, and despite several promising case-reports, this will be the first formal clinical trial of a stem-cell based organ-replacement. Thus, it will provide a level of insight into the real clinical potential for such technologies not previously possible. Through validated functional measures of success/failure over two years' of follow-up, we will determine safety and potential efficacy of an autologous stem-cell based tissue replacement advanced therapeutic medicinal product (ATMP). We will collect data for study by discovery science partners, which will help develop and test hypotheses on the scientific basis of success/failure, and on the behaviour of human stem cells and scaffolds in man. In turn, these will form the basis of discovery and translational grant applications and product improvement. The results will have wide implications for the development of hollow organ-replacements such as those for oesophagus, lung, bowel and vascular disorders. Critically, we also will focus on developing new approaches to reverse translation that will maximise the knowledge and discovery gain from observing the behaviour of cells, stem cells and biological scaffolds (approximating to extracellular matrix) in vivo in man, the "experimental animal of the 21st Century".

Communications Plan

Please outline your plans for engagement, communication and dissemination about your research and its outcomes with the research community and, where appropriate, with potentially interested wider audiences

The investigators regularly speak at public meetings; most lectures at UCL are open to the public by constitution. We will support the BSA National Science and Engineering Week.

We will deliver at least one high impact (NEJM, Lancet) and at least three medium impact papers (Biomaterials, Stem Cells).

We will present at relevant international conferences (TERMIS, ISSCR).

In addition to a dedicated web page, we will maintain updates on ResearchFish, and relevant patient group websites (e.g. Ourairaway.com). PPI group will participate in open meetings and guide public dissemination. The trial will be registered on

the UKCRN portfolio, and feedback to NIHR will be via evidENT.

Exploitable knowledge will be identified and presented at the project meetings prior to any public disclosure/s and the applicants will work with UCLB to pursue appropriate protection on such knowledge.

MAB in particular, and in partnership with our dynamic PPI group, will continue to engage the public at events such as Science Cafés, public dialogues and related events, to explain emerging areas such as stem cells, regenerative surgery and tissue engineering.

This is high profile work and has in the past received a lot of attention from World and UK media, including BBC and CNN. Such contact will be managed by a system set up by PI Birchall whereby both UCL and UCLH/Royal Free media teams receive regular reports and early on develop a media management strategy. This will be communicated also to the MRC media office who will be invited to contribute. Only reputable outlets will be engaged at any time. The goal is responsible reporting, with attempts to highlight any clinical breakthroughs whilst appropriately limiting public expectations. Although it is not possible to prevent individual patients and their immediate circle approaching the media themselves, by close involvement of the patients, with our PPI group's assistance, such 'less controlled' activity may be at least anticipated if not directed in a helpful and ethical direction.

Impact Summary

Impact Summary (please refer to the help for guidance on what to consider when completing this section) [up to 4000 chars]

Who benefits?

2000 UK patients p.a. lose laryngeal function due to trauma or cancer. The main immediate non-academic beneficiaries will be UK patients, their carers and relatives.

In the immediate term, other beneficiaries are both academic and commercial: clinicians, scientists and engineers working in the multidisciplinary environment of regenerative medicine and its robust application to the clinic, life scientists in the field of stem cells and tissue engineering who want to obtain new ways of studying the human organism, and those working at the biotech interface. In the immediate term, benefit will also accrue to the employed researchers, and then the wider UK and international academic communities, public and private education and healthcare sectors, and industry, in which they will be employed.
In the medium- to long-term, beneficiaries include the wider pool of patients with airway disorders, clinicians, the NHS and industry, and ultimately the international healthcare market and needy patients worldwide. Finally, through public engagement, the UK public will also benefit. Also in the longer-term, and if the technology sees it through to commercialisation, University College, London, our host hospital Trusts and the UK economy will benefit. Persons trained in this programme form an invaluable, multidisciplinary reservoir of human resource to help drive and guide the growing RegenMed industry in the UK.

How will they benefit?

The research will have a direct impact on UK health and wealth. The health benefits will come from facilitating UK regenerative medicine by developing the next generation of technologies for the 3d Scaffold and cells growth, characterisation, monitoring and tracking stem cells for clinical applications but also by providing the necessary translational skills to enable the research to directly impact upon the clinic. The outputs will be disseminated widely to all the stakeholder. The ultimate benefit of the research will be a step-change in the production of 3D cell-based scaffold including going from the existing 'open systems' with their reliance on the skill of the operator and a very large manual component towards a closed automatable system. Furthermore, success in this single application will substantially de-risk the field of 3-D tissue-engineered product development by other academic groups and commercial partners.

Whilst the research will concentrate on exploring safety and efficacy of laryngeal replacement implants with immediate outputs at clinical and technology levels, the overall benefits will be far wider and will ultimately impact upon patients with a wide range of organ and tissue replacement needs, such as adults and children with oesophageal and bowel disorders (related hollow organs).

As the research is at the interface between the physical, biological and clinical and management sciences, it offers unique opportunities for training in multidisciplinary research to employed researchers, which will equip them with new skills and give them essential experience for research or related jobs in academia, education, healthcare, and the emerging advanced therapies industry.

What will be done to ensure that they benefit?

We will deliver our Impact Plan through robust, milestone driven and quality controlled management systems, tested by both application to other trials by our highly experienced trials team, and in first-in-human compassionate patients where we demonstrated proof-of-principle of our technology.

We will provide high-quality, tailored and mentored, training to the post-doctoral researchers at the interface between the physical, biological and medical sciences. We have a very strong track record in this arena.

We work seamlessly with UCL Business to explore the potential market for a RegenVOX technology and any potential spin-offs. We embed herein a highly important stream to map out pathways to commercialisation of complex ATMPs.

Summary of Resources Required for Project

Financial resources

Summary fund heading	Fund heading	Full economic Cost	MRC contribution	% MRC contribution
Directly Incurred	Staff	1144739.00	915791.20	80
	Travel & Subsistence	73096.00	58476.80	80
	Equipment	45000.00	22500.00	50
	Other Costs	450316.00	360252.80	80
	Sub-total	**1713151.00**	**1357020.80**	
Directly Allocated	Investigators	248586.57	198869.26	80
	Estates Costs	471908.00	377526.40	80
	Other Directly Allocated	58030.00	46424.00	80
	Sub-total	**778524.57**	**622819.66**	
Indirect Costs	Indirect Costs	1053052.00	842441.60	80
Exceptions	Travel & Subsistence	0.00	0.00	100
	Other Costs	0.00	0.00	100
	Sub-total	**0.00**	**0.00**	
	Total	**3544727.57**	**2822282.06**	

Summary of staff effort requested

	Months
Investigator	38.25
Researcher	304.0
Technician	18
Other	25
Visiting Researcher	0
Student	0
Total	385.25

Other Support

Details of support sought or received from any other source for this or other research in the same field.

Awarding Organisation	Awarding Organisation's Reference	Title of project	Decision Made (Y/N)	Award Made (Y/N)	Start Date	End Date	Amount Sought / Awarded (£)
Medical Research Council	G0902411	REGENVOX. STEM CELL BASED, TISSUE ENGINEERED LARYNGEAL REPLACEMENT.	Y	Y	01/04/2011	31/03/2013	1200000

Staff

Directly Incurred Posts

			EFFORT ON PROJECT							
Role	**Name /Post Identifier**	**Start Date**	**Period on Project (months)**	**% of Full Time**	**Scale**	**Increment Date**	**Basic Starting Salary**	**London Allowance (£)**	**Super-annuation and NI (£)**	**Total cost on grant (£)**
Researcher	Clinical Research Associate	01/04/2013	36	100	CL 7/4	01/08/2013	35596	2806	9294	154953
Researcher	Arnold Darbyshire	01/04/2013	36	100	7 / 37	01/08/2013	37012	2806	9613	154589
Researcher	Carla Carvalho	01/04/2013	36	100	7 / 30	01/08/2013	30122	2806	7814	127995
Researcher	Post Doctoral Researcher	01/04/2013	36	100	7 / 31	01/08/2013	31020	2806	8049	131571
Researcher	Trial Manager	01/04/2013	50	50	7 / 33	01/08/2013	32901	2806	8540	98141
Researcher	Data Manager	01/04/2013	50	20	6 / 24	01/08/2013	25251	2806	5701	29915
Researcher	Clinical Project Manager	01/04/2013	50	20	8 / 40	01/08/2013	40430	2806	10623	47901
Researcher	Programmer	01/04/2013	50	20	7 / 33	01/08/2013	32901	2806	8540	39256
Researcher	Post Doctoral Researcher	01/04/2013	50	100	7 / 39	01/08/2013	39257	2806	10274	218095
Researcher	Head of Statistics	01/04/2013	50	5	9 / 53	01/08/2013	59304	2806	16248	16326
Technician	Samuel Jide-Banwo	01/04/2013	36	50	7 / 30	01/08/2013	30122	2806	7814	63998
Other Staff	Kathryn Fraser	01/04/2013	50	50	5 / 17	01/08/2013	20559	2806	4617	61999
									Total	1144739

Directly Allocated Posts

			EFFORT ON PROJECT							
Role	**Name /Post Identifier**	**Start Date**	**Period on Project (months)**	**% of Full Time**	**Scale**	**Increment Date**	**Basic Starting Salary**	**London Allowance (£)**	**Super-annuation and NI (£)**	**Total cost on grant (£)**
Researcher	Dr R Sheridan	01/04/2013	50	100	9 / 49	01/08/2013	52706	2806	14282	31050
Researcher	Dr L Vallejo-Torres	01/04/2013	50	5	9 / 53	01/08/2013	59004	2806	16248	14652
									Total	45702

Applicants

Role	Name	Post will outlast project	Contracted working week as a % of full time work	Total number of hours to be **charged** to the grant over the duration of the grant	Average number of hours per week **charged** to the	Rate of Salary pool/banding	Cost estimate

		(Y/N)			grant		
Principal Investigator	Professor Martin Birchall	Y	100	1375	7.5	135981	113318
Co-Investigator	Professor Anne GM Schilder	Y	100	344	1.9	0	0
Co-Investigator	Professor Alexander Seifalian	Y	100	315	1.7	112454	21468
Co-Investigator	Dr Mark Lowdell	Y	100	315	1.7	73991	14126
Co-Investigator	Dr Sam Janes	Y	100	113	0.6	107190	7341
Co-Investigator	Professor Anthony Hollander	Y	100	343	1.9	101973	21198
Co-Investigator	Dr Gareth Ambler	Y	100	378	2.1	58246	13344
Co-Investigator	Professor Christopher Mason	Y	100	183	1	86311	9573
Co-Investigator	Dr Tahera Ansari	Y	100	556	3	56080	18897
Co-Investigator	Mrs Susan Tebbs	Y	100	688	3.8	70323	29323
Co-Investigator	Mr Gurpreet Sandhu	Y	100	688	3.8	0	0
						Total	248588

Travel and Subsistence

Destination and purpose		Total £
Outside UK	Conference travel (ISSCR, TERMIS - ML/CC)	1100
Within UK	UK conference travel (ML, CC)	900
Outside UK	Conference travel (SJ)	2000
Within UK	Project travel to London-based meetings (AH)	4240
Within UK	Annual Open Meeting (MB)	6000
Outside UK	Conference travel (ISSCR, TERMIS- MB/AS, CRA)	25000
Within UK	UK conference travel (MB/AS, CRA)	6000
Outside UK	Conference & academic meeting (CTU)	2500
Within UK	Independent data monitoring meetings (CTU)	1760
Within UK	Investigators meeting (CTU)	1000
Within UK	Steering meetings (CTU)	1760
Outside UK	Conference travel (ISSCR, TERMIS - CM, PDR)	10418
Within UK	UK conference travel (CM, PDR)	10418
	Total £	73096

Equipment

Description	Country of Manufacture	Delivery Date	Basic price £	Import duty £	VAT £	Total £	Amount Sought £
Applikon 500ml MiniBio bundle for cell culture	United Kingdom	01/04/2013	45,000.00	0.00	0.00	45,000.00	22,500.00
					Total £	45,000.00	22,500.00

Other Directly Incurred Costs

Description	Total £
PPI group engagement (meetings, travel, accommodation) (MB)	12000
Advertising and recruitment costs (MB)	1000
Bioreactor (AS)	15000
Consumables and project specific costs (Chemical, microscope, analysis, SEM)(AS)	45000
Consumables (ML)	116295
Courier charges (ML)	3300
BioBank set up (ML)	3250
Bioreactors (ML)	5000
CO2 incubator GMP (ML)	9200
Laboratory of Cellular Therapeutics access (RFH) (ML)	25500
Monitored fridge for decell (ML)	1120
Storage in BioBank (ML)	3750
Decellarisation development costs (ML)	17000
Consumables (SJ)	60000
Database (CTU)	12917
Audit (CTU)	300
Archiving materials (CTU)	1000
Laptop/computer (CTU)	3000
Mobile phone (including calls) (CTU)	250
Patient folders (CTU)	300
Secure filing cabinets (CTU)	300
Consumables (CM)	50004
Subject reimbursement costs (MB)	5000
Laptop computer including software and annual upgrades (MB)	3000
NHS Research Costs (UCLH)	56830
Total £	450316

Other Directly Allocated Costs

Description	Total £
Other	9862
Infrastructure Technicians	2466

Total £	12328

Classification of Proposal

(a) Grant Type

Developmental Pathway Funding Scheme	x								

(b) Research Setting

Based on direct patient contact, indicate whether the research involves a particular medical setting such as primary care or secondary care.

Primary									
Secondary	x								
Primary & Secondary									
Emergency									
Other									
None									

Technology Development

Does your work involve Technology development for clinical use: development or adaptation of technologies for diagnosis or therapy, e.g. instrument development for diagnostic or surgical use; development of new techniques, such as photodynamic therapy, for clinical use. Yes

Human Biological Samples

Does your work involve human Biological samples: research which involves laboratory studies on human material which are specifically designed to understand or treat a disease / disorder? NB: basic biomedical research remote from application to a disease / disorder, such as the use of immortalised human cell lines in model biological systems, is excluded. Yes

(c) Stem Cells

Does the research involve the use of Stem Cells or regenerative medicine?

No	
Yes - Adult	x
Yes - Embryonic	
Yes - Both	

(d) Developing Countries

Will the research involve a substantial component in developing countries? If so select those that apply.

Afghanistan		Albania		Algeria		American Samoa		Angola		Argentina		Armenia		Azerbaijan	
Bangladesh		Barbados		Belarus		Belize		Benin		Bhutan		Bolivia		Bosnia and Herzegovina	
Botswana		Brazil		Bulgaria		Burkina Faso		Burundi		Cambodia		Cameroon		Cape Verde	

Central African Republic		Chad		Chile		China		Colombia		Comoros		Congo		Costa Rica					
Croatia		Cuba		Czech Republic		Democratic People's Republic of Korea		Djibouti		Dominica		Dominican Republic		Ecuador					
Egypt		El Salvador		Equatorial Guinea		Eritrea		Estonia		Ethiopa		Fiji		Gabon					
Gambia		Georgia		Ghana		Grenada		Guinea		Guinea-Bissau		Guyana		India					
Indonesia		Iran (Islamic Republic of)		Iraq		Ivory Coast (Cote D Ivoire)		Jamaica		Jordan		Kazakhstan		Kenya					
Kiribati		Kyrgyzstan		Lao People's Democratic Republic		Latvia		Lebanon		Lesotho		Liberia		Libyan Arab Jamahiriya					
Lithunia		Madagascar		Malawi		Malaysia		Maldives		Mali		Marshall Islands		Mauritania					
Mauritius		Mayotte		Mexico		Micronesia, Federated States of		Moldova		Mongolia		Morocco		Mozambique					
Myanmar		Namibia		Nepal		Nicaragua		Niger		Nigeria		Northern Mariana Islands		Oman					
Pakistan		Palau		Panama		Papua New Guinea		Paraguay		Peru		Philippines		Poland					
Romania		Russian Federation		Rwanda		Saint Kitts and Nevis		Saint Lucia		Saint Vincent and The Grenadines		Samoa		Sao Tome And Principe					
Senegal		Serbia and Montenegro		Seychelles		Sierra Leone		Slovakia		Solomon Islands		Somalia		South Africa					
Sri Lanka		Sudan		Suriname		Swaziland		Syrian Arab Republic		Tajikistan		Tanzania		Thailand					
The Democratic Republic of the Congo		The former Yugoslav Republic of Macedonia		Timor-Leste		Togo		Tonga		Trinidad and Tobago		Tunisia		Turkey					
Turkmenistan		Uganda		Ukraine		Uruguay		Uzbekistan		Vanuatu		Venezuela		Viet Nam					

Central African Republic		Chad		Chile		China		Colombia		Comoros		Congo		Costa Rica					
Croatia		Cuba		Czech Republic		Democratic People's Republic of Korea		Djibouti		Dominica		Dominican Republic		Ecuador					
Egypt		El Salvador		Equatorial Guinea		Eritrea		Estonia		Ethiopa		Fiji		Gabon					
Gambia		Georgia		Ghana		Grenada		Guinea		Guinea-Bissau		Guyana		India					
Indonesia		Iran (Islamic Republic of)		Iraq		Ivory Coast (Cote D Ivoire)		Jamaica		Jordan		Kazakhstan		Kenya					
Kiribati		Kyrgyzstan		Lao People's Democratic Republic		Latvia		Lebanon		Lesotho		Liberia		Libyan Arab Jamahiriya					
Lithunia		Madagascar		Malawi		Malaysia		Maldives		Mali		Marshall Islands		Mauritania					
Mauritius		Mayotte		Mexico		Micronesia, Federated States of		Moldova		Mongolia		Morocco		Mozambique					
Myanmar		Namibia		Nepal		Nicaragua		Niger		Nigeria		Northern Mariana Islands		Oman					
Pakistan		Palau		Panama		Papua New Guinea		Paraguay		Peru		Philippines		Poland					
Romania		Russian Federation		Rwanda		Saint Kitts and Nevis		Saint Lucia		Saint Vincent and The Grenadines		Samoa		Sao Tome And Principe					
Senegal		Serbia and Montenegro		Seychelles		Sierra Leone		Slovakia		Solomon Islands		Somalia		South Africa					
Sri Lanka		Sudan		Suriname		Swaziland		Syrian Arab Republic		Tajikistan		Tanzania		Thailand					
The Democratic Republic of the Congo		The former Yugoslav Republic of Macedonia		Timor-Leste		Togo		Tonga		Trinidad and Tobago		Tunisia		Turkey					
Turkmenistan		Uganda		Ukraine		Uruguay		Uzbekistan		Vanuatu		Venezuela		Viet Nam					

For this phase I/II clinical trial, ten consenting patients conforming to entry criteria will be drawn from those presenting to the London Airway Service based at UCLH NHS Foundation Trust. Inclusion criteria are patients aged 18-65years' old with severe (Myer-Cotton Grade 3/4) laryngotracheal stenosis who have exhausted conventional therapies. Due to the small number, we cannot guarantee equal numbers of male and female participants; in practice, 70% of patients with these problems are female. We anticipate a range of ethnic backgrounds, reflecting our referral patterns.

Recruitment will be by a specialist nurse and a trained patient (from PPI group) jointly, using REC-approved consenting.

Exclusion criteria are:

1. Pregnant or lactating women.
2. Those unable to provide informed consent.
3. Severe chronic pulmonary problems, as determined by an independent expert respiratory physician
3. Patients with active/uncontrolled chronic inflammatory conditions such as Wegener's and sarcoid as determined by an independent rheumatologist
4. Any previous cancer within 10 years (except basal cell carcinoma of the skin, adequately treated carcinoma-in-situ of the uterine cervix or locally treated laryngeal carcinoma without spread)
5. Other co-existing medical condition such that life expectancy is less than two years

Procedures to be performed are, firstly, a day-case, general anaesthetic (GA), retrieval of bone marrow and bronchoscopic bronchial epithelial cells for culture and differentiation as part of the finished implant and, secondly, a general anaesthetic operation via the neck to remove scar tissue and replace with the implant. Cells surplus to requirements will be stored for later study, as will those taken by cytology brushings and biopsy at follow-up flexible, day-case bronchoscopies performed at six time points over the ensuing two years of follow-up. The UCL Biobank (Director Co-I Lowdell) is fully equipped and accredited for the purposes of storing and retrieving such samples for discovery research and therapeutic use.

Animal Research

Would the project involve the use of vertebrate animals or other organisms covered by the Animals (Scientific Procedures) Act?	Yes	No✓
If yes, what would be the severity of the procedures?	Mild	
	Moderate	
	Substantial	
Please provide details of any areas of substantial or moderate severity:		

Animal Species

Does the proposed research involve the use of non-human primates?	Yes	✓No
Does the proposed research involve the use of dogs?	Yes	✓No
Does the proposed research involve the use of cats?	Yes	✓No
Does the proposed research involve the use of equidae?	Yes	✓No

Please select any other species of animals that are to be used in the proposed research.

Fish	Rabbit
Amphibian	Cow
Reptile	Pig
Bird	Sheep
Rat	Poultry
Mouse	
Other Rodent	
Guinea Pig	

Genetic and Biological Risk

Would the project involve the production and/or use of genetically modified animals?	Yes	✓	No
If yes, will the genetic modification be used as an experimental tool, e.g., to study the function of a gene in a genetically modified organism?	Yes	✓	No
And will the research involve the release of genetically modified organisms?	Yes	✓	No
And will the research be aimed at the ultimate development of commercial or industrial genetically modified products or processes?	Yes	✓	No
Would the project involve the production and/or use of genetically modified plants?	Yes	✓	No
If yes, will the genetic modification be used as an experimental tool, e.g., to study the function of a gene in a genetically modified organism?	Yes	✓	No
And will the research involve the release of genetically modified organisms?	Yes	✓	No
And will the research be aimed at the ultimate development of commercial or industrial genetically modified products or processes?	Yes	✓	No
Would the project involve the production and/or use of genetically modified microbes?	Yes	✓	No
If yes, will the genetic modification be used as an experimental tool, e.g., to study the function of a gene in a genetically modified organism?	Yes	✓	No
And will the research involve the release of genetically modified organisms?	Yes	✓	No
And will the research be aimed at the ultimate development of commercial or industrial genetically modified products or processes?	Yes	✓	No

Implications

Are there ethical implications arising from the proposed research? No

Provide details of what they are and how they would be addressed [up to 1000 characters]

Approvals

Have the following necessary approvals been given by:			
The Regional Multicentre Research Ethics Committee (MREC) or Local Research Ethics Committee (LREC)?	Yes	No✓	Not required
The Human Fertilisation and Embryology Authority?	Yes	No	Not required✓

The Home Office (in relation to personal and project licences, and certificates of designation)?	Yes	No	Not required✓
The Gene Therapy Advisory Committee?	Yes	No	Not required✓
The UK Xenotransplantation Interim Regulatory Authority?	Yes	No	Not required✓
Administration of Radioactive Substances Advisory Committee (ARSAC)?	Yes	No	Not required✓
Other bodies as appropriate? Please specify.			
MHRA	Yes	No✓	
NHS R&D	Yes	No✓	

OTHER INFORMATION

Reviewers

1	Name	Address	Town	Email Address
Dr Peter Belafsky		UC Davis Health System	Sacramento	peterb@ucdvoice.org
Area of Expertise				
Relationship with Reviewer				
Reason for Reviewer		Airway expert with interest in regenerative medicine; published on outcomes of airway surgery; recent research into MSC for tongue paralysis; PhD in epidemiology.		

Reviewers

2	Name	Address	Town	Email Address
Dr Tracy Grikscheit		Pediatric Surgery	Childrens Hospital Los Angeles	tgrikscheit@chla.usc.edu
Area of Expertise				
Relationship with Reviewer				
Reason for Reviewer		Developing tissue-engineered bowel replacements for children; familiar with the challenges of developing complex hollow organ ATMPs and their use with stem cells		

Reviewers

3	Name	Address	Town	Email Address
Dr Anthony Atala		Richard H Dean Biomedical Building	Winston Salem	aatala@wakehealth.edu
Area of Expertise				
Relationship with Reviewer				
Reason for Reviewer		Father of surgical tissue engineering with over 12 years' experience of clinical trials for bladder replacement in children		

13th November, 2012

Dr. Jonathan Pearce
Translational Programme Manager
Medical Research Council
14th Floor, 1 Kemble St
London WC2B 4AN

Dear Jonathan,

Re: Birchall et al., RegenVOX, MR/K017292/1: response to reviewers' feedback.

Please find uploaded the above application to DPFS/DCS as requested and in approved format. With respect to the specific points raised by referees to the preliminary application, please see responses below. In addition, the panel wished to know about our consideration of competing technologies, and especially the FP7 project NEOtrachea. Our response to this is in contained section 4 of the main form.

1. **Reviewer 1 (1-105QO6):** no comments to address.
2. **Reviewer 2 (1-ZYIYE):** The proposal will follow-on sequentially from the two years of RegenVOX1 (late preclinical studies).
3. **Reviewer 3 (1-ZYJ8F):** No comments to address.
4. **Reviewer 4 (1-ZYJ8H):**

Quality, point 1. Recruitment will be over 8 months and is feasible as demonstrated in the full proposal (6.13); we have increased detail surrounding the primary outcome measure (6.2); deaths are not expected in this sample of patients and we are not expecting to lose any patients (drop-outs) during the follow-up period. If loss or deaths do occur, the patient will be replaced from a list of identified, willing patients conforming to entry criteria. Since 90% of problems in airway reconstruction occur during the first six months, it is unlikely that follow-up time would have to be extended by more than three months, and then likely only for one patient, which could be accommodated within present costs (no cost extension).
Quality, point 3. These patients are used to frequent travelling and repeated, strenuous rounds of investigation and treatment, similar to or more intense than that proposed here, in order to maintain their airways and prostheses and some quality of life. Our patient group, not surprisingly therefore, has not raised the number or type of investigations and visits as a problem. We expand on optimisation of recruitment strategies in 6.2i.
Research environment. The role of the discovery science consultant Hollander is expanded upon in the justification for funding paper uploaded. Further details of numbers of complex airway patients are given in 6.13. The team sees a wide range of patients, but about half cause upper tracheal and laryngeal stenosis/malacia, of which 60% are traumatic/iatrogenic, 15% inflammatory and 25% idiopathic.
Impact: Continuous quality improvement and cost reduction form part of milestone 2, and proposed methods expanded upon (5.1). Wider implications for organ and tissue regenerative technologies are addressed in 4.4 and 7.6.
Ethics: We agree safety and risk are paramount in this project. We wished to keep to a single primary outcome measure here for simplicity and statistical purposes, and the one selected was determined

Prof Martin Birchall, Professor of Laryngology, Consultant Head and Neck Surgeon
Royal National Throat, Nose and Ear Hospital, 330 Gray's Inn Road, London, WC1X 8DA
Tel: 0207 915 1308
Fax: 0207 833 9480
E mail: m.birchall@ucl.ac.uk
PA: a.oliphant@ucl.ac.uk

by patients and clinicians together. However, safety remains a key outcome measure and will be monitored intensely by our Independent DMC.

5. **Reviewer 5 (1-ZYJ8I)**

Quality. Point 1. Based on the outcomes of research in the MRC funded 'RegenVOX1' project, the product herein is based entirely on biologic scaffolds.
Point 2. Serum levels of anti-scaffold donor antibodies will be assessed immediately pre-implantation and at 6, 12, 18 and 24 months post-implantation (See schedule, Table 1). Donor HLA profile will be supplied by NHS Blood and Transplant per protocol.
Point 3. The autologous epithelial cells used will be those that proliferate *in vitro* from airway biopsies. These all are basal cells (keratin $14/5^{+}$), but we several primary human samples in air-liquid interface cultures also showed characteristic differentiation into ciliated and Clara cells. Thus, we deliberately call our starting cells 'progenitors' as they proliferate and have *in vitro* multi-potency, but we accept that cannot be rigorously defined as 'stem cells' presently.
Point 4. The pre-clinical work supporting the product specifications for our clinical tracheal implants demonstrated that MSC and MSCC do not survive the prolonged exposure to media required for growth of airways epithelial cells. However, we consistently maintained primary cultures of airway epithelia cells on decellularised tracheal scaffold after transfer to media which support MSC growth and differentiation. These data were replicated *in vitro* and *in vivo* in pigs using human cells on decellularised hemilarynx. Our SOPs for GMP manufacture describe the isolation and expansion of primary autologous airway epithelial cells and their seeding onto decellularised human larynx. After adherence and further *ex-vivo* expansion on the scaffold within our disposable bioreactor for 2-3 days, the medium is changed and the scaffolds seeded with expanded MSC/MSCC. MSC/MSCC adherence, ingress and additional proliferation occur over 2-3 days. Our *ex-vivo* culture, GLP porcine and clinical tracheal implant work show that epithelial cells survive this additional period well.
Point 5. Selection criteria have been clarified in section 6.2
Point 6. A key part of this proposal is the determination of ways of maximising discovery science opportunities. It may be possible to supplement brushings with biopsies in well-healed patients, and in all cases blood samples will be taken and all samples stored in the UCL biobank (Director, Co-I Lowdell). The material will be studied by discovery science partners once appropriate hypotheses have been developed and proposals accepted by the PMG, however an possible example that we are presently exploring under separate funding is the use of superparamagnetic nanoparticles to trace cell fate.
Point 7. We will store a range of sizes of larynx to ensure best fit. Desired size and shape will be assessed using CT reconstructions and endoscopy.
Point 8. The term laryngotracheal profile has been withdrawn.
Environment. We have no conflicts to declare.
Ethics. Eligible patients will be any patient who would normally qualify for NHS treatment, without socioeconomic restriction. There will be no costs to participants and we request only those costs which are in excess of those normally expected to manage patients with these disorders.
Resources. Sandhu is now a Co-I with costs included. Sandhu and Birchall will jointly be responsible for clinical care of these patients, who will spend two weeks in hospital, and two nights postoperatively in HDU.

Many thanks for your attentions,

Yours sincerely

Martin Birchall, MD, FRCS, F MedSci
Professor of Laryngology and Consultant ENT Surgeon
UCL and UCLH

Prof Martin Birchall, Professor of Laryngology, Consultant Head and Neck Surgeon
Royal National Throat, Nose and Ear Hospital, 330 Gray's Inn Road, London, WC1X 8DA
Tel: 0207 915 1308
Fax: 0207 833 9480
E mail: m.birchall@ucl.ac.uk
PA: a.oliphant@ucl.ac.uk

DPFS/DCS: FULL FORM

Section 1: Project Summary

1.1 Title (max 150 characters) [same as Je-S Project Title]
RegenVOX: phase I/II clinical trial of stem cell based tissue engineered laryngeal implants

1.2 Technical Summary (max 2000 characters) [same as Je-S Technical Summary]
There are no satisfactory conventional solutions for patients with end-stage laryngeal stenosis, which can result from trauma or after cancer resection. This has profound impacts on quality of life, especially swallowing, breathing and talking. Based on our 'first-in-human' successes with tracheal implants[1,2], we developed an autologous stem cell and biologic scaffold based partial laryngeal implant to correct severe structural disorders. In preclinical studies, this was biocompatible in rats, and safe and effective in pigs (human cells in immunosuppressed animals). We have developed robust processes for production of cells, scaffold, bioreactor and implant within our fully Good Manufacturing Practice (GMP) licensed cell therapy facility. UCLH hosts the national airway service, which has the largest pool of potential recipients in Europe, and skilled clinical staff. **We propose** a 50 months' project to encompass a phase I/IIa clinical trial of customized stem cell based laryngeal implants in ten patients with severe laryngeal stenosis who have exhausted conventional therapeutic options, and with two years' follow-up. **Milestones will be:** 1. Obtain necessary authorisations, and perform first implant 2. Complete recruitment and submit processes for IP assessment 3. First two patients attain 6- and 12-month efficacy targets; cost-reduction achieved 4. Completion of follow-up, reporting to MRC and MHRA and publication in high impact journal **Specific aims will be:** Months 1-12, Optimisation of recruitment strategies, preparation of final trial documentation, PSF; final testing of production process, QC/RC, bioreactor construction; REC/R&D/CTA approvals Months 13-20, Recruitment, Intervention, Monitoring Months 21-44, Follow-up, Continuous improvement of production processes; Use of tissue/blood data by discovery science partners to develop and test hypotheses on behaviour of human stem cells and scaffolds in vivo in man. Months 45-50, Analysis, Reporting, commercialisation and/or phase III trial plans; reverse translational grant applications.

1.3 Project Duration and Cost [same as in Je-S submission]	
Proposed start date (dd.mm.yyyy)	01.04.2013
Proposed duration of award (Months)	50
Project fEC (£000s)	
RC contribution (£000s)	
Project Partner Contribution (£000s)	0

Section 2: Investigator Details

2.1 Principal Investigator [same as Je-S Principal Investigator]	
Name	Martin BIRCHALL
Post Held	Professor of Laryngology

Section 4: Need and Proposed Solution

4.1 What is the health, clinical or product development need you are seeking to address? (max 150 words)

Conventional solutions to advanced structural disorders of the larynx are a major unmet medical need[3]. The larynx protects the airway during swallowing, regulates breathing, and permits voice: all fundamental human functions. Over 2000 UK patients p.a. lose laryngeal function due to trauma or cancer[4]. Patients with these problems require frequent hospitalisation. 1300 NHS patients p.a. require full or partial laryngectomy. Conventional treatment is sub-optimal for many: 'organ-preservation' treatments have high morbidity, mortality, and can leave a functionless larynx resulting in significant disability. However, a regenerative-medicine solution using a living tissue-engineered replacement could transform their functional outcome (replacing vocal cord with vocal cord instead of scar) and in some cases even avoiding the need for a total laryngectomy. The goal is to advance a safe, clinically efficacious and cost effective therapy suitable for routine NHS use, resulting in improved quality of life for patients and carers, whilst reducing overall costs.

4.2 What is your proposed solution to this need and how long will it take to develop? (max 150 words)

The product will be a partial laryngeal replacement construct, composed of a decellularised human donor scaffold re-seeded with autologous mesenchymal stem cell derived chondrocytes externally and autologous mucosal-derived epithelial cell sheets internally. Preclinical development, funded by MRC TSCRC, is highly advanced and we have achieved proof-of-principle through compassionate-use tracheal implants using similar technology. However to complete the development, we need a further year of trial preparation plus 32 months of recruitment and follow-up and a final six months of data analysis and reporting. Parallel streams will be reverse translation hypothesis generation, cost of goods analysis and business modeling.

4.3 Who are the end users of your proposed solution, how many of them are there, and what benefits does your solution provide them? (max 250 words)

Conventional solutions to advanced structural disorders of the larynx are sub-optimal. Patients with these problems require frequent hospitalisation. Of the 2000 people p.a. with laryngeal cancer in the UK[4], 800 undergo local resection leaving permanent defects in the vocal cords and hoarseness. The 500 most advanced cases have their larynx removed completely. The remainder undergoes chemoradiotherapy which achieves good cure rates, but has high morbidity, 5% mortality, and can leave a functionless larynx. There are a further 200 patients p.a. with equally severe problems due to trauma or chronic inflammation. A regenerative solution providing anatomical restoration of the larynx would improve the results of resection (e.g. by replacing vocal cord with vocal cord instead of scar), avoid some laryngectomies, and lower the threshold for selecting surgery over chemo-radiotherapy, thus reducing morbidity. For many patients, adequate breathing is only possible via a tracheostomy (tube/hole in the neck), which severely affects quality of life, especially speaking and swallowing, and is costly to maintain. Our solution provides a once-only therapy of a life-time functional living replacement, allowing patients to lead tracheostomy-free lives, without repeated visits to hospital for laser and other maintenance treatment. They will have improved breathing, swallowing and speech. By deliberately developing the replacement larynx to be manufactured at an economically viable cost of goods (through ongoing discussions with NICE and hospital trusts), overall healthcare costs will be reduced. Patients and carers will be able to retain jobs, and thus both groups may contribute positively to UK society and wealth.

4.4 Are there further needs that could be addressed by your proposed solution and/or by components of your proposed solution (i.e. is it a platform technology)? (max 100 words)

Department	UCL Ear Institute
Institution	UCL

2.2 Co-Investigators [same as Je-S Co-Investigators]	
Name	**Institute/Organisation/Company**
Mark LOWDELL	UCL
Sam JANES	UCL
Alex SEIFALIAN	UCL
Chris MASON	UCL
Gareth AMBLER	UCL
Anthony HOLLANDER	University of Bristol
Tahera ANSARI	Northwick Park Institute for Medical Research
Guri SANDHU	UCL
Anne SCHILDER	UCL
Susan TEBBS	UCL

2.3 Industrial Partners	
Name	**Institute/Organisation/Company**

2.4 Collaborators	
Name	**Institute/Organisation/Company**
Kelly CHAPMAN	*Ourairaway.com* patient group
Reza NOURAEI	London Airway Service

Section 3: Host Institute Technology Transfer Office Contact

3.1 Host Institute Technology Transfer Office Contact	
Name	Rebecca PAULRAJ
Post Held	Business Manager
Department	UCL Business

This will be the first formal clinical trial of a stem-cell based organ replacement (as opposed to the few patients who have been treated on a named-patient basis[5]). Thus, it will provide a level of insight into the real clinical potential for stem cell/tissue engineering combined technologies. The results will have wide implications for the development of hollow organ-replacements such as those for oesophagus, bowel and vascular disorders. We will also develop new pathways for maximising discovery science and health economic benefit from complex regenerative medicine therapies (a reverse translational route map), with important generic benefits for scientists and clinicians.

Section 4: Need - Competitiveness

4.5 Who (in academia or industry) is developing/has developed competing solutions? (max 75 words)

The Kyoto-Fukushima group (Omori, Sato[6,7]) have used synthetic scaffolds to achieve partial laryngeal replacement. Based on work performed by the Paris-Lille group (Marquette, Martinod[8,9]) with preserved homograft aorta, the Boston group (Zeitels[10]) have used similar technology for partial laryngeal replacement. The Strasbourg group (Debry[11,12]) is using a metal device for total laryngeal replacement. The Karolinska group has published on the decellularisation of the larynx and is experienced in tracheal replacement[13].

4.6 What are the competing solutions and what is their developmental status? (max 75 words)

The Kyoto-Fukushima group used polypropylene mesh to replace part of the larynx in one patient (2008[6]), and reported a coated polypropylene construct in animals (2010[7]). Zeitels' homograft solution is localised to one centre and is not in clinical trials (2012[10]). Debry's ENTegral metal (titanium[11]) valved implant, patented by ProTip is in clinical trials in France for laryngectomy patients (2012[12]). Karolinska group has not progressed work on the larynx since 2010[13], and has leadership problems.

4.7 What are the shortcomings of competing solutions and what is the advantage of your proposed solution? (max 150 words)

The Boston group's aortic allografts (non-living) do not replicate the contours of a normal larynx (required for acceptable voice and swallowing outcomes, about which their report is vague[10]), an essential prerequisite for a transformative therapy and one our living technology through its innate ability to remodel does possess. They also do not regenerate cartilage in tracheal reconstruction (lower structural integrity[8,9]) and epithelial re-growth is slow[8,9] (clinically unfavourable). In our preclinical experiments, cartilage regeneration was observed and epithelial re-growth swift and complete, including over the replaced vocal cords. The Japanese and Strasbourg solutions are based on conventional materials used in reconstructive surgery (polypropylene, titanium[6,7,11,12]). History repeatedly has shown such materials to integrate poorly into airways and propagate infection[14]. Our principle advantage is that the once-only therapy is regenerative and not an inferior substitution requiring a life-time of maintenance and/or early failure. None of these potentially competing solutions are truly regenerative.

4.8 What is the anticipated cost of your proposed solution both at launch and at scale? How does this compare with competing solutions? If the cost is anticipated to be greater than competing solutions, why will your solution be favoured? (max 100 words)

Laryngeal replacement is an unmet medical need. Whilst it is likely that the non-living homografts will result in an overall lower cost offering (potentially in the order of £5-10,000 based on similar

homografts e.g. CryoLife, USA[15]), the technology lacks the necessary performance that will transform patients lives whilst having the potential for significant complications including needing expensive stenting. We estimate (based on our tissue-engineered airway first-in-man studies) that our non-optimised product preparation is in the order of £20,000. However, our cost of goods will reduce with technological improvements likely to be generated by this project. Milestone 2 sees us reducing costs by a minimum of 25% through continuous improvement techniques, giving even better cost-benefit performance.

Section 5: Rationale and Evidence

5.1 What is the rationale and supporting evidence for why your proposed solution will meet the targeted need? (max 1250 words)

The approach is based on the technology developed by a number of members of the team to produce living tissue-engineered airways. RegenVox includes the leader of the team which implanted the first stem-cell based airway replacement[2]. This has been followed by similar implants in children, all for compassionate reasons[1]. In the reported patient, a 4.5cm decellularised human tracheal scaffold was repopulated with autologous epithelial cells and chondrocytes of mesenchymal stem cell (MSC) origin. At four year follow-up (unpublished), she is well with normal lung function and a healthy graft. Our first child patient has reached 30 months post-implantation and is at school and growing normally with no regular clinical intervention[1]. His graft vascularised quickly and had normal epithelium by eight months (Fig.8). A second child underwent a successful implant in 2011, but died of non-graft related causes soon afterwards. Her graft was healthy and vascular at time of death, however and, importantly, her case afforded an opportunity to 'field-test' the GMP procedures, protocols and quality control measures included in the present project (paper in preparation). These 'first-in-human' successes demonstrate that such constructs have therapeutic potential, but as these were urgent, compassionate use applications, the method was applied before all the necessary regulatory preclinical work had been completed. However, the technology had not been extended to produce larynx.

Based on our clinical successes and non-GMP/GLP pre-clinical data[19,20], in an MRC-TSCRC funded project, we developed a stem-cell based laryngeal implant (RegenVOX) that was demonstrated to be safe and effective in GLP (Good Laboratory Practice) studies. We produced standard operating procedures (SOPs) for the clinical preparation and seeding of human MSC and MSC-derived chondrocytes (MSCC) on scaffolds and have developed customised disposable bioreactors (Fig.6) as well as GMP transport and storage processes. We determined the optimal source of autologous epithelial cells (bronchial, Fig.4a), and prepared SOPs for seeding these onto scaffolds (Fig.4b). We developed a new, very fast, effective method for laryngeal decellularisation (Fig.5) and results proved safe and biologically inert in rats and pigs (Fig.7).

Meetings with MHRA determined that the appropriate model for work leading to a Clinical Trials Authorisation (CTA) would be human cells in immunosuppressed pigs. We gave 16 pigs seeded laryngeal implants (Fig.7b). Animal survival to 2 months was 81%. Decellularised scaffolds showed mild inflammatory responses, but, importantly, clear evidence of remodelled cartilage (Fig.7e; unlike aortic allografts, see above). In all, endoluminal repair was excellent with glandular and interstitial regrowth (Fig.7e). Computerised tomographic (CT, Fig.7c) scans showed patent airways. Human cells were identifiable at the implant site for four weeks (Fig.7d). Thus, we have shown biocompatibility, safety and efficacy in pigs. As part of the same MRC funded project, we developed SOPs for MSC immunophenotyping (QC/RC), preparation, isolation and *ex vivo* expansion of mesenchymal stromal cells from haematopoetic progenitor cells prepared from marrow (HPC-M) and seeding of MSC on laryngeal scaffolds. We have sourced GMP compliant/qualified reagents for all stages of production, and Draft Batch Manufacturing Record sheets have been developed. These SOPs and records were field-tested during production of the implant for the second child described above, permitting further refinement and demonstration of utility in the clinic. All of this documentation will form part of the Product Specification File to be submitted to MHRA early in the present project and means we are very well placed to secure CTA at the milestone proposed.

In comparative studies, epithelial cells of bronchial origin were superior to those of nasal origin in terms of cellular proliferation and their ability to differentiate into ciliated and goblet cells. The cultures achieve confluence with formation of tight-junctions in air-liquid interface cultures and on decellularised laryngeal tissue (Fig.4a). A protocol is now in place that can deliver the cell number required within four weeks of bronchial biopsy plating. Cells can be

stored in liquid nitrogen and re-expanded if required without loss in proliferative capacity.

We found that we were able to substantially accelerate the process of decellularisation by using a variable pressure based method allowing for removal of all nuclear material within the overlaying muscle and cartilage over a 7 day period (Fig.5). The technique preserved anatomy, including critically the vocal cords, and biomechanical strength including the structural integrity of the collagen in a quarter of the time taken by conventional protocols such as that published by the Karolinska group above. Both the muscle and cartilage was assessed individually and showed that <50ng/mg DNA remained at the end of the process, whilst 60% GAG retention was observed compared with native larynx. Again, this method was successfully field tested in the production of a robust, easily recellularised, tracheal graft for the second child above. After four weeks subcutaneous implantation of non-recellularised laryngeal scaffold prepared in this way in rats, only mild inflammatory responses were observed not amounting to clinical concern and with no evidence of rejection (Fig.7a).

We have developed a bioreactor system which comprises a non-disposable central monitoring core connected to disposable bioreactors for individual products. These are customised for the recellularisation of the laryngeal implants herein and disposability facilitates GMP process standards and reduces costs (Fig.6).

We have performed a highly detailed healthcare and manufacturing economic analysis of the entire process of treating patients on a one-off basis using tissue-engineered airway produced using the same underpinning platform technology as this application. We have investigated the complete process by breaking it into a number of discrete but interacting components: 1] Cell harvesting, 2] Donor graft decellularisation and tracheal graft creation, 3] MSC expansion, 4] Surgical implantation, and 5] Aftercare. We plan to use the same approach for the RegenVOX project. The data we have collected from the tissue-engineered airway work and analysed (n=3) has enabled us to produce extremely accurate costings for the present proposal. It will also provide a unique baseline for the health economics and commercialisation studies needed for RegenVOX if we are to meet our goal of a safe, clinically efficacious and cost effective therapy that can be routinely deployed in the NHS. The overall aim is to produce a transformative therapy whilst reducing the overall cost of patient care to the NHS - aims that from our prior economic analysis would appear achievable. We will also use the data to secure sustainability for the long-term availability of the therapy either through licensing to a commercial organization or via imbedded NHS GMP units. We will use quality improvement techniques, including critical path analysis, PDSA (plan-do-study-act) cycles and root-cause analysis to incrementally improve efficiency of production and clinical processes and, critically, to reduce cost (Milestone 3).

In summary, our safety, efficacy, histology data, and published clinical success suggest that we are perfectly placed to proceed to the next logical translational step, a phase I/II clinical trial of stem-cell based partial laryngeal implants based on decellularised scaffolds in needy patients.

DPFS/DCS: FULL FORM

Section 6: Deliverability - Objective and Approach

6.1 What is the project's primary objective/deliverable? In the case of applications from MRC Institutes and Units, applicants need to describe how the proposed research builds on, but is distinct from, their agreed quinquennial programme of research. (max 100 words)

The primary objective of this study is the timely delivery of a Phase I/II (safety and early indicator of efficacy) clinical trial of stem-cell based, tissue-engineered laryngeal implants in patients with severe irreversible structural disorders of the larynx unresponsive to conventional treatment. Deliverables will be: 1. GMP product production processes for a tissue-engineered partial laryngeal replacement implant; 2. Safety and efficacy data in a phase I/II trial in ten patients; 3. Economic and business modeling (orphan indication) for the complete process of producing and implanting the constructs; 4. New pathways for reverse translation involving complex stem cell product trials.

6.2 What is the project's starting point and what approach is proposed to reach the objective? Why have you chosen this approach over alternatives? How have you engaged end-users and/or downstream intermediaries in the development of your plan? For clinical studies, please include details of and rationale for (1) study design, (2) study participants, (3) study endpoints, (4) dose, (5) anticipated effect size and (6) analysis plans (max 1250 words)

The project's starting point:

This project (Fig.1) is designed to provide a novel, stem cell and tissue engineered, solution to partial laryngeal replacement in patients following cancer and trauma, an 'orphan' clinical need which causes considerable loss of quality of life for patients. We start with - the results of an MRC-TSCRC funded project described above, which demonstrated safety and potential efficacy in pigs and permitted the development of SOPs for cell, scaffold and construct production, as well as novel decellularisation and bioreactor technology. We also start with seminal clinical experience of similar technology applied to one adult and two children with life-threatening tracheal disorders[1,2]. The latter demonstrated proof-of-principle in human subjects and permitted successful field-testing and incremental improvement in our protocols, and generated important economic data.

Conventional alternatives:

Laryngeal reconstruction with either flaps or aortic homografts[10] has failed to deliver satisfactory airways, voice and swallowing, and thus quality of life, for patients with advanced laryngeal structural disorders after surgery or trauma. For many, life is preserved

only through the use of tracheostomies, T-tubes or stents, all of which carry sequelae of infection and discomfort, and possible complications of erosion, blockage and bleeding. Thus overall quality of life is often low even though the overall cost to the healthcare system, the patient and their carers is disproportionately high. A solution which avoids such prosthetic means of maintaining the airway would be highly preferable and also permit effective voice production and swallowing, all basic elements of human existence. Competitor technologies are described above and are early very stage, sub-optimal and/or poorly developed: rival groups are not at our stage of readiness to translate a safe functional product let alone cost-effectively.

End-user engagement:
Our product has been developed in collaboration with the London Airway Team. Established in 2009 by PI Birchall, Co-Applicants Sandhu, Janes, Collaborator Nouraei *et al.*, this is the national, and leading international, referral centre for patients with complex disorders of the larynx and trachea. We have also engaged with *Ourairaway.com*, a new UK-based airway disorders patient group established by patients for patients, and including collaborator Chapman who will also be a member of the Trial Steering Committee (TSC). The MHRA have been consulted regularly and their advice, together with the expressed views and needs of patients, has substantially shaped the present application and the work leading up to it.

Phase I/IIa Clinical Trial:
This trial will be run under the management of the new UCL Clinical Trials Unit (Co-I Tebbs), and will also form a key part of the UCL ENT NIHR Clinical Trials Programme (evidENT, Co-I Schilder). We have developed and validated clinical outcome measures (Collaborator Nouraei [16,17]) and recruitment processes for clinical trials using existing patient cohorts. Statistical preparation is complete, and a protocol and case record forms (CRF) under development. Schedule of Activities is shown in Table 1. Key elements of the trial protocol are:

a. Inclusion criteria. Patients aged 18-65y old with severe (Myer-Cotton Grade 3/4) laryngo-tracheal stenosis, who have exhausted conventional therapies, presenting to the London Airway Service.

b. Exclusion criteria.

- Pregnant or lactating women.
- Those unable to provide informed consent.
- Severe chronic pulmonary problems, as determined by an independent expert

respiratory physician

- Patients with active/uncontrolled chronic inflammatory conditions such as Wegener's and sarcoid as determined by an independent rheumatologist
- Any previous cancer within 10 years (except basal cell carcinoma of the skin, adequately treated carcinoma-in-situ of the uterine cervix or locally treated laryngeal carcinoma without spread)
- Other co-existing medical condition such that life expectancy is less than two years

c. Recruitment. By specialist nurse and a trained patient jointly, REC-approved consenting.

d. Procedures. Procedure 1 is a day-case, general anaesthetic (GA), retrieval of bone marrow and bronchoscopic bronchial epithelial cells. Procedure 2 is a GA operation via the neck: access, removal of scar tissue, implantation of implant, temporary tracheostomy, inpatient care for up to two weeks.

e. Follow-up. See Table 1 for schedule. There will be 2 years' follow-up within project, as recommended by MHRA, including key Milestones at 6 and 12 months' post-implantation. These patients are used to frequent travelling and repeated, strenuous rounds of investigation and treatment, similar to or more intense than that proposed here, in order to maintain their airways and prostheses and some quality of life. Our patient group, not surprisingly therefore, has not raised the number or type of investigations and visits as a problem.

f. Primary outcome measure: Efficacy: attainment of prosthesis-free airway (i.e. lacking tracheostomy/T-tube/stent) at 12 and 24 months. This will determine 'success or failure' of the clinical component of the project. Post hoc process analysis will focus on technical improvements that will feed into a phase III trial ('success') or that may explain 'failure'.

g. Secondary outcome measures: Safety: mortality, morbidity, development of anti-donor antibodies; Efficacy: time to prosthesis-free airway, narrowest part (CT >70% normal Cotton 1 equiv.), >70% predicted PEFR, flow-volume ratio, effort physiology, symptoms, quality of life (SF36); Resource use (see below).

h. Power and statistical analysis (Co-I statistician Ambler): Success is defined by the (binary, yes/no) primary outcome measure above. With ten patients, assuming an 80% success rate based on preclinical and first-in-human (tracheal) data, the probability of achieving seven or

more 'successes' is 88%. Descriptive statistics will be used to describe the baseline characteristics and the secondary outcomes of the patients; means and standard deviations, and proportions will be used for numerical and categorical variables respectively. The success rate will be estimated using proportions and a corresponding exact confidence interval will be calculated. Missing data is not anticipated in this small sample.

i. Patient and public Involvement (PPI). We have established a PPI group with patients from patient organisation Ourairaway.com. This group will help developed recruitment processes and literature, contribute to lay summaries and updates; provide communication with patient groups; provide patient focus to outcome measures; assist in dissemination of the findings (see below). Optimisation of recruitment strategies will utilise qualitative research techniques developed by PI Birchall for the CRUK EaStER surgical trial[18]. The research fellow and PPI group will develop prototype recruitment methodology which will then be applied. Transcripts of recruitment conversations will be analysed for themes and used for incremental improvement. A survey of clinician views and beliefs will be carried out by the research fellow and nurse via the BLA and used to improve referral rates.

The Investigational Medicinal Product

This is a tissue-engineered partial laryngeal implant manufactured as an Advanced Therapy Medicinal Product (TEP) under our MHRA MA (IMP). Our novel, fast decellularisation protocol will be used to prepare laryngeal scaffolds from human donor larynxes purchased under an established contract with NHS Blood and Transplant (NHSBT), following training of retrieval teams by RegenVOX surgeons. Autologous MSC, MSCC and respiratory epithelial cells will be produced according to the protocols above and seeded onto the scaffolds within our dedicated disposable bioreactors, in a system monitored automatically. Following the successful application of in-process quality control (QC) and release criteria (RC), implants will be released by the manufacturing GMP laboratory at the Royal Free Hospital to the UCLH Pharmacy under existing agreements and supplied directly to the operating theatre team for implantation in the prepared and consented recipient (Fig.2).

6.3 Please identify the extent to which your approach is timely and innovative. For example, does it push boundaries over and beyond current leading-edge approaches, or is it applying existing technologies in new areas? (max 100 words)

To our knowledge, this will be the first formal clinical trial of a stem-cell based organ-replacement. It will provide a new level of insight into the real clinical and commercial potential for such technologies. Through validated functional measures of success/failure

over 2 years' follow-up, we will determine safety and potential efficacy of a stem-cell based ATMP. Data released to discovery science partners will help develop and test hypotheses on the scientific basis of success/failure, and the behavior of human stem cells and scaffolds in man. In turn, these will inform discovery and translational grant applications and product improvement.

6.4 Where appropriate, please justify the use of animals or patients and the numbers of animals, samples, patients, etc tested. (max 150 words)

Efficacy is determined by whether a patient attains prosthesis-free airway (i.e. no tracheostomy/T-tube/stent) at 6 and 12 months. Success is defined by whether this is achieved for at least 70% of recruits. With ten patients, the probability of achieving seven or more 'successes' is 88%. This assumes that each patient has an 80% chance of attaining prosthesis-free airway, a value based on our preclinical and first-in- human data.

Given seven 'successes', a one-sided 90% confidence interval suggests that success rate is at least 45%. If eight or nine successes are observed, the lower bound for success rate becomes 55% or 66% respectively. Deaths and drop-outs are not expected in this sample of patients. If these do occur, the patient will be replaced from a list of willing patients conforming to entry criteria.

6.5 What are your plans for disseminating the results of the research? Are there any restrictions on this dissemination and, if so, what are these? (max 100 words)

The investigators regularly speak at public meetings; most lectures at UCL are open to the public by constitution. We will support the BSA National Science and Engineering Week.
We will deliver >1 high impact (NEJM, Lancet) and>3 medium impact papers (Biomaterials, Stem Cells).
We will present at relevant international conferences (TERMIS, ISSCR).
In addition to a dedicated web page, we will maintain updates on ResearchFish, and relevant patient group websites (e.g. Ourairaway.com). PPI group will participate in open meetings and guide public dissemination. The trial will be registered on the UKCRN portfolio, and feedback to NIHR will be via evidENT.

Section 6: Deliverability - Project and Risk Management

6.6 Who will the project manager be? If already identified, please provide details of their experience in managing projects similar to that proposed. If not yet identified, please provide a job specification for the project manager role and your recruitment strategy. (max 150 words)

Rose Sheridan, a member of the UCL Translational Research Office initially established through MRC funding, will be the named project manager for RegenVOX. She will draw on her 20 years industrial and project management experience in Biotechnology and Pharma in conjunction with experience gained from ongoing Class III medical implant projects at UCL for which she is currently providing project management support. Additionally, a clinical trials project manager will be appointed by the UCL CTU (t.b.a.).

PM Sheridan will be the principal interface with MRC. She will ensure timely and comprehensive reporting, regular liaison and project meetings covering all clinical and non-clinical aspects of the project. She will act to co-ordinate all members of the project team and ensure they are aware of milestones, meetings and other obligations. She will identify problems early and notify the PI and Co-PIs so these can be addressed as early as possible.

6.7 Please provide details of the track record of the project team in delivering projects similar to that proposed to include, where relevant, details of who will manage outsourced relationship(s) and what experience they have of managing relationships of this kind? (max 250 words)

PI Birchall: Project Management. Co-led the teams that delivered the world's first stem cell based organ implant in an adult and a child and the World's second laryngeal transplant.
Co- Lowdell: GMP ATMP production. Director Cell Therapy and Biobanking; UCL Senior Lecturer in Haematology; cellular therapeutics specialist.
Co-I Janes: Epithelial science. Wellcome Clinical Senior Fellow; developed assays for epithelial cell growth, differentiation and survival; Thoracic Oncology Investigator of the Year, 2010.
Co-I Schilder: Trial design and delivery. Director ENT Clinical Trials Programme; NIHR Rsearch Professor; Prof Paediatric Otorhinolaryngology; PI on numerous clinical trials of surgery.
Co-I Ambler: Study design, analysis, interpretation and reporting. UCL Senior Lecturer in Medical Statistics; works with UCL/PRIMENT CTUs, 10y experience in phase I, II, III trials.

Co-I Mason: Health economics, commercialisation. UCL Prof. Regenerative Medicine Bioprocessing; 20y experience ATMP commercialisation.
Co-I Seifalian: Bioreactor design and production. Multi-award winning Prof. of Nanotechnology. **Co-I Hollander:** Discovery science consultant, maximizing the scientific potential from the trial, identifying key partners (e.g.Crick).
Co-I Ansari: Novel decellularisation process that is 4x faster than earlier methods.
Co-I Sandhu: Surgical aspects of design. International expert in complex airway surgery; thesis on laryngeal reconstruction.
Co-I Tebbs: UCL CTU liaison, study design, set-up and regulatory overview.
Collaborator Nouraei: ENT ACF; PhD on outcome measures in complex airway care.
Collaborator Chapman: Trained patient PPI representative of *Ourairaway.com*.
Independent Expert Advisor Domayne-Hayman: Commercial Advisor. Previously CEO Stabilitech, Senior Development Manager Celltech.
Independent Data Monitor Rutter: Director Clinical Research, Cincinnati Children's Hospital Medical Center; homografts in airway reconstruction.

6.8 What are the key risks to delivering the project, how likely are these to occur and what would their impact be? How will these risks be managed? (max 250 words)

Trial Steering Committee (TSC, Fig.3) and Independent Data Monitoring Committee (IDMC) will be established. IDMC accesses all blinded/aggregate data, reports to TSC on recommendations for premature closure and safety. High level, then detailed, risk assessments at pre-/post-award letter points to assess safety, management and reputational risk are reviewed by CTU Quality Management Group. Milestone slippage is reported to MRC, but most can be accommodated by no-cost extension (see 'Milestones').
Milestone 1 risk is minimised by considerable MRC-funded preparatory work, and frequent MHRA liaison. Team is experienced in negotiating REC/R&D hurdles. LCT submitted 8 successful ATMP CTAs, supports 7 ATMP trials, manufactures 4 ATMPs as unlicensed medicines. UCL has two full-time ATMP regulatory officers.
Milestone 2 recruitment risk is covered in 6.2.
It will be clear six months post-implantation of the first few patients whether Milestone 3 will be hit[17], permitting identification of technical risks to efficacy at an early point. Unexpected SAE/Rs or interventions will be considered when preparing for phase III trial/market authorisation. Failure to meet Milestones, or if safety and efficacy are demonstrated ahead of schedule, early reporting/termination of the trial will be discussed with MRC.
Milestone 4 allows ample time to complete reporting. Given our high profile work, length of follow-up and the publication level of analogous work the risks of not publishing at highest level are small.
For risks posed by competitors, see Section 4. PM and team will horizon-scan for new

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developments and any relevant information, papers or conference presentations and present at PMG meetings.

Section 6: Deliverability – Resource Requirements and Environment

6.9 What resources (materials, methods, data, people, infrastructure, outsourced tasks etc) are needed to undertake the proposed project? Please specify the need, the costs and the timelines of usage/employment with respect to achievement of the stated milestones? (max 300 words)

We require funds to support the development of final production processes and supporting documentation. This requires personnel, including essential scientific staff and a quality assurance manager, and laboratory costs for work on scaffolds, cells and bioreactors. Delivery of the products requires sourcing appropriate materials, including human donor scaffolds, and also some extra equipment (specifically a holographic microscope for quality control work and a bioreactor monitoring system). We require funds for a clinical trials support team (manager, IT, PPI and statistical support) to prepare and submit materials for obtaining relevant permissions, prepare trial documentation, initiate, manage and monitor the clinical trial. This team will also perform data collation, management and statistical analysis and assist with reporting. We require support for a research fellow to assist recruitment of patients and organise clinical visits, investigations, consenting, follow-up and operating theatre sessions. The necessary clinical costs over and above normal NHS care are also requested for patients enrolled, and include outpatient, investigation, patient travel and accommodation and inpatient/operating theatre costs. Support is required for health economic and commercialisation work packages, and for supporting PPI engagement and integration. Funds for project management include the costs of a PM (Sheridan) and support, consumables, meetings and travel costs, computing, presentation, conference attendance and travel, publication costs.

6.10 Are these resources in hand? If not, what gives you confidence that they will be available when required? Include manufacture of novel therapeutics where appropriate (max 150 words)

We have the facilities and project team in place to deliver this project given the above resources. Required equipment and materials are easily accessed from reputable sources. Clinical resource is already present but will improve with the centralization of complex airway services, and consequent upgraded provision, on the UCLH site in 2013. Likewise, UCL and the Royal Free Hospital are presently establishing a Centre for Applied Regenerative Sciences at the Royal Free campus with new space and infrastructure support, based around the work of the co-applicants.

6.11 Please provide a high-level justification for the requested resources, in terms of the overall needs of the project (a more detailed explanation can be given in the "Justification of Resources" document). (max 300 words)

This is a substantial project given the needs of bringing a complex cell-based ATMP from bench to bedside. Although we have performed a significant amount of preparatory work, we do not underestimate the amount of laboratory and CTU work required to obtain all necessary permissions and have the production processes fine-tuned, including dry-runs, for the start of the trial at the end of year one. The nature of this product requires us to employ parallel teams to deal with cell, tissue and bioreactor parts of production, as well as to prepare for and run a clinical trial. Thus, we in effect roll together costs from both laboratory science and clinical trials in order to achieve our very high impact, but clearly, given our team and track record, tractable goals. This combination, although costly, is necessary to achieve our goals and to path-find for other UK regenerative medicine technologies that will follow. The clinical costs herein are entirely within the scale of complex treatments, such as aortic grafting, chemotherapy or stereotactic radiosurgery, within the National Health Service. Furthermore, our costs (and prototype methodology) have been field tested in three compassionate use cases. Although a final combined product and clinical cost of around 60,000 per patient seems expensive, compared to the continuing costs of maintaining airways in these patients using conventional means, which can amount to millions per patient over time, the costs of our product are rapidly recouped if implantation is successful, as indeed would be the costs of this project itself.

6.12 Describe how the scientific or clinical environment(s) in which the research will be undertaken will increase the chances of success. Including, where relevant, how the research will benefit from facilities provided by the host institution or established clinical infrastructure such as Biomedical Research Units/Centres, Clinical Research Facilities or patient cohorts. (max 150 words)

UCL demonstrates more bench-bedside translation regenerative technologies than any other centre in the UK. UCLH is a leading Foundation Trust with commitment to a substantial investment in a new head and neck disorders hospital build on site.
ULCH BRC, in which regenerative medicine is a key theme, funded the Clinical Research Facility which provides a state-of-the-art base for recruitment, high-resolution digital endoscopy and follow-up for our patients. BRC funding also pump-primed our CTU, providing support to prepare this application and which will be running the trial.
Co-I Schilder, the World's leading ENT clinical triallist, was awarded £1.6m NIHR Research Professorship. She has established a unique trials resource and network for ENT, evidENT, based at UCLH-RNTNEH.
We also have an array of world class laboratories: Janes' specialises in the biology of airway stem cells; Lowdell's produce cell therapy medicinal products for clinical trials. Mason's is the largest international bioprocessing group.

6.13 For clinical studies, please outline the recruitment strategy and target recruitment rate. Include evidence of feasibility where appropriate (max 200 words)

The London Airway Service (LAS), established in 2009 by Co-I's Birchall, Sandhu, is the national and leading international referral centre for patients with complex airway disorders, providing the richest possible source of patients for this trial. An unexpected, but welcome, off-shoot of the LAS is *Ourairaway.com*, an airway disorders patient group which has provided, and will continue to provide, invaluable PPI input to this project. We are developing optimal recruitment strategies, and patients will themselves be involved in consenting processes to ensure maximum understanding and engagement by potential recruits (see 4.1), as well to prioritise patient-focused outcomes. There are >200 new NHS patients p.a. referred to this service *per annum*, of whom 30 are potentially eligible. In practice, we have already identified at least five ideal candidates, which means that with a low figure of 25% recruitment, we would expect to recruit the remaining 5 patients within an eight month window (hence the length of the recruitment period). However, we expect a higher rate of recruitment than this, given our focus on recruitment methodology.
Additionally, we will advertise the trial through the newly established British Laryngological Association (BLA), so ensuring an increase over baseline of recruits from around the UK.

Section 7: Downstream Project Support

7.1 What are the major downstream hurdles that will need to be overcome if the project is to meet its ultimate aims? (max 100 words)

We need to identify the correct path to commercialisation for this highly novel product. We envisage that this will involve some form of licensing by a host Trust(s), here likely to be Royal Free London and UCLH FTs. However, the precise route to market needs detailed exploration and this is a key part of this project. Indeed, RegenVOX will in this sense represent pathfinder technology for the marketing of other complex, cellularised ATMP organ and tissue-replacements developed in the UK.

7.2 Will any new technologies, processes, etc - such as a new manufacturing process - be required to overcome these hurdles? If so, please describe them and what gives you confidence that they will be available when required? (max 100 words)

We have all the prototype technologies and processes in place, and have field tested and refined them in three compassionate use settings in critically ill patients. Whilst there is further refinement to come, and we cannot anticipate every technical hurdle ahead, we have built in resources and time which permit us the flexibility to perform essential continuous improvement as the project progresses. Hence it is important to maintain a significant laboratory staff until the end of the first year of follow-up, so that the eventual processes and product are as close to a final marketable implant as possible.

7.3 How will the project be sustained post DPFS/DCSs support to enable it to meet its ultimate aims (i.e. what is your exit strategy)? What sources of subsequent funding/potential partners are available to you? What criteria will need to be met in order to access these funds/partnerships and how will the planned programme of work help to meet these criteria? (max 400 words)

The commercialisation strategy for RegenVOX will be developed through a comprehensive piece of path-finding health-economics/business planning led by Co-I Mason herein (see justification for details). However, our high-level draft plans for sustainability/continuation and implementation are as follows:

1. We will produce sufficient data to permit the issuance of a product license by MHRA based on the evidence of this project and its MRC-funded predecessor. At this point, we will present a business case for the establishment of a service at one or both of our host NHS FTs, supported by any combination of NHS, industrial and VC funding.
2. However, if MHRA do not agree to a product license straight away and request a Phase III trial (unlikely from preliminary discussions), we will seek NHS, commercial partners and apply as a consortium to NIHR and/or MRC. Our rapidly developing trials (evidENT) and clinical (British Laryngological Association, BLA) networks make such a multicentre trial for treatment of an uncommon disorder feasible in a way that could not have been foreseen a few years ago. This trial would be designed, as here, by a combination of UCL CTU and evidENT through NIHR CCRN ENT specialty group (Chair Co-I Schilder), with clinical input from the LAS and BLA (Chair, Co-I Sandhu).
3. Potential commercial partners for such a trial would include NHSBT, with whom we already have a supply agreement and who specialise in the provision of decellularised human tissues and organs, or a new spin-out company created through UCLB. However, other options will be considered in our commercialisation work stream herein.

7.4 Have you made initial contacts with potential downstream funders/partners and, if so, who are they and what is the status of your discussions? If not, by which specific timepoint do such links need to be in place and with whom? (max 100 words)

See 7.3. We are working with the Royal Free London FT Board to create a new Centre for Applied Regenerative Science (CAReS). They have indicated interest in the commercial

potential of our products. UCLB assisted us in the search for IP and other business considerations below and represent valuable partners. We hold regular talks with NHSBT who have a major interest in developing their in-house business around decellularised human tissues/organs in a similar way to that made successful by Dutch 'Euro Tissue Bank' (http://www.eurotissuebank.nl/euro-tissue-bank/). Finally, through UCLB we are developing a network of investors/VC specialising in the emergent RegenMed field.

7.5 Have you sought an industrial partner for this project? If not, why did you feel that an industrial partnership was not appropriate (stage of project, type of project, nature of the commercial opportunity, etc)? If you have not managed to find a partner, why (stage of project, type of project, nature of the commercial opportunity, etc)? *Note that inclusion of an industrial partner is not mandatory and we recognise that this will not be appropriate for all projects.* (max 300 words)

A complex ATMP for an orphan indication is unlikely to attract the interest of a major pharmaceutical company. It is much more appropriate herein to have a working model based on NHS investment in provision of the implant as a new service to UK and, indirectly, the rest of the world. However, various combinations of investor are also possible, and all of these will be explored as part of our health economics and commercialisation theme herein (Co-I Mason).

7.6 Are there other potential non-academic beneficiaries, in addition to your identified end-users, who might benefit from your intervention or from advances made in its development? What are your plans for engaging with these other potential beneficiaries? (max 300 words)

Claude Bernard said that "science proceeds through revolution, not addition". The proposed work is truly disruptive in the sense that we are not just exploring a whole new approach to treating illness, but the clinical, economic, social, commercial and scientific environment in which it will flourish. Other potential beneficiaries of this work are multiple.

1. NHS institutions, and other healthcare systems, will learn what is required to nurture and then exploit game-changing technologies with the capacity to provide a one-off complex treatment for long-term health and wealth gain.
2. We will provide a wake-up call for UK surgeons and pointers as to how transplant and other services may be reorganised to best exploit the fruits of the RegenMed revolution.
3. Finding a commercial pathway to clinic for complex device implants and cellularised ATMPs is a major advance in itself and is of considerable generic benefit to the emergent UK RegenMed industry and thereby to UK Plc.
4. We will develop mechanisms for patients and the public to engage with and help direct the development of regenerative medicine products, and contribute to the public understanding of stem cells and regenerative medicine approaches to health and healthy living.

The surgical procedures used in this project are known, the hollow organ tissue processing methodology has been documented, disposable bioreactors for MSC preparation and GMP grade or GMP-compatible consumables, including larynxes supplied by NHSBT, are procured off the shelf and are not subject to any third party IP restrictions.

8.6 Do the applicants and collaborator(s), if such exist, have rights to use the Delivery Technologies? If yes, please specify how such rights have been acquired. If not, how does the applicant intend to secure such rights. (max 200 words)

The work that underlies this application was performed at UCL/NPIMR and no restrictions on use exist with reference to this data and thus the applicants are free to develop this technology. Preliminary key word searches described in Section 8.2 identified no freedom to operate issues with respect to additional third party IP.

8.7 Do any of the academic applicants have a direct or indirect interest (consultancy, shareholding, options, etc) in the commercial owners of Delivery Technologies? If so, what is the nature of their interest and how are conflicts of interest being managed? (max 100 words)

None of the academic applicants have any direct or indirect interests in the Core Technologies.

Management and Exploitation of Knowledge

8.8 Please describe your strategy for protecting the Knowledge. (max 200 words)

Exploitable knowledge will be identified and presented at the project meetings prior to any public disclosure/s and the applicants will work with UCLB to pursue appropriate protection on such knowledge. All new inventions will be presented to UCLB's invention review panel and a decision to patent will be made based on the novelty and inventive step in light of the prior art and commercial/clinical value. Advice will be sought from UCLB's external patent attorneys where necessary. There is potential for IP to be generated during the performance of this study that will support the approach being developed by the applicants. This includes results, know-how and/or inventions around the specific MSC tissue generation and hollow organ processing procedures.

8.9 Please describe your plans and strategies regarding further development and exploitation of the Knowledge. (max 200 words)

During the clinical trial phase of the project, UCLB will work closely with the applicants to ensure that the commercial focus of the project is considered at every stage. It is envisaged that post-completion of this study, a centre for clinical excellence in this methodology will be set up at UCL with a view to treating a wider cohort of the relevant clinical population.
A commercial collaboration with an industrial partner may be sought to further develop the product portfolio to other organ types. Potential partners in this field may be the current suppliers of the disposable bioreactors and cell feeds or one of the leading institutes interested in this field.
UCLB is confident that a partnership could be secured with a commercial entity based on the clinical package generated during this clinical trial. Our aim would be to work with this partner to leverage further funding through the TSB, EU, FP7 or NIHR funding sources to conduct the next phase of clinical testing followed by implementation as a routine procedure on the NHS and with partner health services worldwide.

Restrictions on Exploitation of Knowledge

8.10 Will the academic applicants have the right to exploit the Knowledge developed by their activities at the end of the project? If there are any restrictions or limitations on exploitation, please describe them. (max 100 words)

There are no foreseen restrictions on the applicant's rights to exploit the Exploitable

Section 8: Intellectual Property (IP)

It is expected that this section should be completed in partnership with your Institution's Technology Transfer Office (TTO), or equivalent, and failure to do so may prejudice your application. *Note that the generation of protectable intellectual property is not an essential requirement for this scheme; projects that will not generate patentable materials but that have the potential to provide health benefits are accepted on an equal basis.*

Core Technologies

8.1 Please list all existing technologies (together with patent application/patent numbers where applicable) that will be further developed as part of your proposed project ("Core Technologies"). (max 100 words)

The Core Technology to be further developed and trialed under this proposal is the RegenVOX stem cell tissue engineered laryngeal replacement technology (methodology and development process) developed during the initial (preclinical) RegenVOX study funded by the MRC-TSCRC.

8.2 Please provide a summary of the most relevant documents in relation to Core Technologies identified through a prior art search. (max 200 words)

Extensive keyword searches of Patent Lens, Espacenet, Pubmed and Google were conducted by UCL Business PLC (UCLB). Search terms included laryngeal replacement, MSC graft seeding, hollow organ grafts/transplants. No patents were identified that could prevent the future commercialisation or wider clinical use of this process.
There are numerous articles relating to the initial compassionate-use tracheal implant operations performed on two patients - as per sections 4.2 and 5.1, performed present team members. The clinical trial documented in this application will be instrumental in generating a larger set of clinical data to support the case for approval and implementation within the NHS and other health services with a view to offering this replacement therapy to a larger cohort of patients.

8.3 Do the applicants and collaborator(s), if such exist, have rights to work on the Core Technologies? If yes, please specify how such rights have been acquired. If not, how does the applicant intend to secure such rights? (max 200 words)

The work that underlies this application pertaining to the use of decellularised human donor scaffolds, re-seeding with autologous MSC and the customised GMP manufacturing processes required was all performed at UCL and partner NPIMR. No restrictions on use or future commercialisation (if applicable) exist with reference to this data and the applicants are free to develop this technology as any arising IP from the initial study would have been or will be subject to patent applications in the name of UCL/NPIMR. Preliminary key word searches described in Section 8.2 identified no freedom to operate issues with respect to additional third party IP.

8.4 Do any of the academic applicants have a direct or indirect interest (consultancy, shareholding, options, etc) in the commercial owners of Core Technologies? If so, what is the nature of their interest and how are conflicts of interest being managed? (max 100 words)

None declared.

Delivery Technologies

8.5 Please list the most important tools (materials, methods and data) that will be used in the project but will not form a part of the project end result and for which you need rights to ("Delivery Technologies").

The surgical procedures used in this project are known, the hollow organ tissue processing methodology has been documented, disposable bioreactors for MSC preparation and GMP grade or GMP-compatible consumables, including larynxes supplied by NHSBT, are procured off the shelf and are not subject to any third party IP restrictions.

8.6 Do the applicants and collaborator(s), if such exist, have rights to use the Delivery Technologies? If yes, please specify how such rights have been acquired. If not, how does the applicant intend to secure such rights. (max 200 words)

The work that underlies this application was performed at UCL/NPIMR and no restrictions on use exist with reference to this data and thus the applicants are free to develop this technology. Preliminary key word searches described in Section 8.2 identified no freedom to operate issues with respect to additional third party IP.

8.7 Do any of the academic applicants have a direct or indirect interest (consultancy, shareholding, options, etc) in the commercial owners of Delivery Technologies? If so, what is the nature of their interest and how are conflicts of interest being managed? (max 100 words)

None of the academic applicants have any direct or indirect interests in the Core Technologies.

Management and Exploitation of Knowledge

8.8 Please describe your strategy for protecting the Knowledge. (max 200 words)

Exploitable knowledge will be identified and presented at the project meetings prior to any public disclosure/s and the applicants will work with UCLB to pursue appropriate protection on such knowledge. All new inventions will be presented to UCLB's invention review panel and a decision to patent will be made based on the novelty and inventive step in light of the prior art and commercial/clinical value. Advice will be sought from UCLB's external patent attorneys where necessary. There is potential for IP to be generated during the performance of this study that will support the approach being developed by the applicants. This includes results, know-how and/or inventions around the specific MSC tissue generation and hollow organ processing procedures.

8.9 Please describe your plans and strategies regarding further development and exploitation of the Knowledge. (max 200 words)

During the clinical trial phase of the project, UCLB will work closely with the applicants to ensure that the commercial focus of the project is considered at every stage. It is envisaged that post-completion of this study, a centre for clinical excellence in this methodology will be set up at UCL with a view to treating a wider cohort of the relevant clinical population.
A commercial collaboration with an industrial partner may be sought to further develop the product portfolio to other organ types. Potential partners in this field may be the current suppliers of the disposable bioreactors and cell feeds or one of the leading institutes interested in this field.
UCLB is confident that a partnership could be secured with a commercial entity based on the clinical package generated during this clinical trial. Our aim would be to work with this partner to leverage further funding through the TSB, EU, FP7 or NIHR funding sources to conduct the next phase of clinical testing followed by implementation as a routine procedure on the NHS and with partner health services worldwide.

Restrictions on Exploitation of Knowledge

8.10 Will the academic applicants have the right to exploit the Knowledge developed by their activities at the end of the project? If there are any restrictions or limitations on exploitation, please describe them. (max 100 words)

There are no foreseen restrictions on the applicant's rights to exploit the Exploitable

Knowledge generated as all new results and intellectual property surrounding this methodology will vest with UCL.

8.11 Will the licensee or assignee of the Knowledge have freedom to operate it? If not, please list the relevant patents/patent applications including their owners and explain why you think they are relevant. (max 100 words)

Yes, we anticipate that an exploiting party will have freedom to operate. There are no relevant patents that have been identified that may be cited to prevent this from happening.

8.12 If needed for exploitation of the Knowledge, will the applicant be able to pass rights to Core Technologies to the exploiting party (max 200 words)

The applicants hold no patent applications around the Core Technology as yet. The concept for the compassionate use indication has been documented extensively in the media and in publications. However, any new developments surrounding the preparation of the donor organ, tissue engineering (GMP bioreactor modifications, feeds & nutrient preparation & delivery) and seeding processes generated during the original study and this one will be subject to patent applications. Assignment and licensing of said technology may take place at a future date if required for exploitation.

8.13 If needed for exploitation of the Knowledge, will the applicant be able to pass rights to Delivery Technologies to the exploiting party? (max 100 words)

It is anticipated that some delivery technologies will be widely available for purchase directly from the manufacturers. The rights to any new patent technologies developed during the course of this study and the preceding one may be licensed to a suitable commercial entity for exploitation at a future date.

8.14 Any other points pertinent to protection or exploitation of knowledge not addressed in the sections above? (max 100 words)

None

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Section 9: Clinical Considerations

Please complete this section if your application includes clinical (human) research. Applicants who are not proposing human studies do not need to complete this section.

9.1 Are there any ethical issues which might complicate or prolong ethics approval? Please give particular consideration to any potential safety risks. (max 300 words)

We observe the 2005 Research Governance Framework for Health and Social Care. Cells/scaffolds are stored under HTA license awarded to Laboratories for Cell Therapy (Co-I Lowdell). Scaffolds are supplied under agreement from NHS Blood and Transplant, retrieved under the national framework governing the use of organs and tissues for research and clinical purposes, including traceability. An application for a CTA from MHRA forms part of milestone 1 in this project, as do parallel REC, UCLH R&D applications. We have found no difficulty in obtaining larynxes from transplant donors so far, since the incision required for retrieval is non-disfiguring and low in the neck. These can be stored as above, so we will have an ample bank of organs by the start of recruitment. Human cells used for process development are obtained as by-products of the therapeutic human stem cell programme at LCT, whilst epithelial cells are obtained from routine bronchoscopies at UCLH under a separate LEC approval (Co-I Janes). All laboratory staff working with human cells and tissues are appropriately trained and immunised. The sponsor for this trial is UCL through the Joint Research Office, and as such, UCL will provide legal cover for the trial in the event of unexpected problems and challenges. We have considered a wide range of potential sequelae and complications resulting from the use of our implants and these are being incorporated into our consenting process, with the assistance of our PPI representatives, to reduce risk and maximise patient understanding.

9.2 Please provide details of the study sponsor and any relationship with a commercial partner. Please note that MRC is not the sponsor of university research. (max 100 words)

We have no relationship with a commercial partner. Sponsorship will be provided by UCL through the Joint Research Office (JRO). The sponsor (UCL) will provide indemnity and support as required by the UK Statutory Instruments for Clinical Trials with special considerations for ATMPs. A number of the sponsor functions including QA,QC, regulatory oversight, trial governance, risk assessment and monitoring of mitigation strategies and will be delegated to the UCL CTU.

9.3 Please provide information on the status of required regulatory approvals. Please give particular consideration to any potential safety risks or ethical issues. (max 300 words)

The Medicines and Healthcare Products Regulatory Agency (MHRA) will consider risks as a central part of their assessment process when we submit our product specification file in year 1. Our implants proved safe in preclinical trials and closely related technology has provided new tracheae to adults and children, saving and lengthening lives. Our discussions with MHRA so far suggest that this safety data will be sufficient for the granting of a CTA for this trial.

Application for Research Ethics Committee approval (REC) will be in parallel with MHRA application. The concern of the REC is for patient safety and ethical practices, and we will address their questions in full. Our team is highly experienced in dealing with these issues and we do not expect any major delays or barriers to approval given our preclinical and first-in-human success to date.

9.4 Please summarise the NHS support costs (note that NHS support costs should be listed in the "Additional Costs Proforma: NHS Support and Treatment costs" and attached separately to the application) (max 100 words)

DPFS/DCS: FULL FORM

These are those necessary for recruitment, investigation, implantation surgery and associated inpatient costs, outpatient follow up, including tests and bronchoscopy and trouble-shooting. We have costed these accurately based on our first-in-human experiences in adults and children receiving tracheal implants. The costs requested represent those in excess of costs which would normally be incurred in the care of these patients.

DPFS/DCS: FULL FORM

Annex I: Outsourcing

I.1	Who are you considering contracting to undertake the outsourced work? (max 100 words)
N/A	

I.2	What is each party contributing to the delivery of the project plan and what task(s) are they responsible for? Is the contribution unique or could a similar contribution be made by an alternate group/organisation? (max 150 words)

I.3	Please describe how the proposed outsourcing either enables the planned research to be undertaken or enables the planned research to be undertaken to the required quality or timescale. (max 150 words)

I.4	Please describe the agreement between the parties regarding management, ownership and rights to the project generated intellectual property. (max 100 words)

I.5	Do any of the participating academics have a direct or indirect interest (consultancy, shareholding, options, etc) in the industrial contractor(s)? If so, how are conflicts of interests between the parties being managed? (max 150 words)

Annex II: References

II.1 References (max 700 words)

1. Elliott MJ, DeCoppi P, Speggiorin S, Roebuck D, Butler C, Samuel E, Crowley C, McLaren C, Fierens A, Vondrys D, Cochrane L, Jephson C, Janes S, Beaumont N, Cogan T, Bader A, Seifalian A, Hsuan J, Lowdell M, Birchall M. Two-year follow up of a stem cell based, tissue engineered tracheal replacement in a child. Lancet, 2012 Sep 15;380(9846):994-1000.

2. Macchiarini P, Jungebluthe P, Go T, Asnaghi A, Rees LEN, Cogan T, Dodson A, Martorell J, Bellini S, Dickinson S, Hollander A, Mantero S, Conconi MT, Birchall MA. The first clinical application of a tissue-engineered airway transplant. *The Lancet*. 2008; Dec 13;372:2023-30.

3. Fishman JM, De Coppi P, Elliott MJ, Atala A, Birchall MA, Macchiarini P. Airway tissue engineering. Expert Opin Biol Ther. 2011 Dec;11(12):1623-35.

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5. Lowdell MW, Birchall M, Thrasher AJ. Use of one-off, compassionate use, advanced therapy medicinal products (ATMP) as a safe and valid alternative to animal models for pre-clinical data for clinical trial submissions? Lancet, 2012 Jun 23;379(9834):2341.

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10. Zeitels SM, Wain JC, Barbu AM, Bryson PC, Burns JA. Aortic homograft reconstruction of partial laryngectomy defects: a new technique.Ann Otol Rhinol Laryngol. 2012 May;121(5):301-6.

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12. http://clinicaltrials.gov/ct2/show/NCT01474005?term=protip&rank=1

13. Baiguera S, Gonfiotti A, Jaus M, Comin CE, Paglierani M, Del Gaudio C, Bianco A, Ribatti D, Macchiarini P. Development of bioengineered human larynx. Biomaterials. 2011 Jul;32(19):4433-42.

14. Toomes H, Mickisch G, Vogt-Moykopf I. Experiences with prosthetic reconstruction of the trachea and bifurcation. Thorax. 1985 Jan;40(1):32-7.

15. Brown JW, Ruzmetov M, Rodefeld MD, Vijay P, Darragh RK.Valved bovine jugular vein conduits for right ventricular outflow tract reconstruction in children: an attractive alternative to pulmonary homograft. Ann Thorac Surg. 2006 Sep;82(3):909-16.

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DEVELOPMENTAL PATHWAY FUNDING SCHEME: MILESTONE FORM

Section 1: Project Summary

1.1 Title (max 20 words) [same as EAA Title of Application]
RegenVOX: phase I/II clinical trial of stem cell based tissue engineered laryngeal implants

1.2 Abstract (max 200 words) [same as EAA Title of Application]
There are no satisfactory conventional solutions for patients with end-stage laryngeal stenosis, which can result from trauma or after cancer resection. This has profound impacts on quality of life, especially swallowing, breathing and talking. Based on our 'first-in-human' successes with tracheal implants1,2, we developed an autologous stem cell and biologic scaffold based partial laryngeal implant to correct severe structural disorders. In preclinical studies, this was biocompatible in rats, and safe and effective in pigs (human cells in immunosuppressed animals). We have developed robust processes for production of cells, scaffold, bioreactor and implant within our fully Good Manufacturing Practice (GMP) licensed cell therapy facility. UCLH hosts the national airway service, which has the largest pool of potential recipients in Europe, and skilled clinical staff. We propose a 50 months' project to encompass a phase I/IIa clinical trial of customized stem cell based laryngeal implants in ten patients with severe laryngeal stenosis who have exhausted conventional therapeutic options, and with two years' follow-up. Specific aims will be: Months 1-12, Preparation for and commencement of clinical trial Months 13-20, Recruitment, intervention Months 21-44, Follow-up, continuous improvement of production processes, reverse translation Months 45-50, Reporting, publication, commercialisation

Section 2: Applicant Details

2.1 Lead Applicant [same as EAA Lead Applicant]	
Name	Martin BIRCHALL
Post Held	Professor of Laryngology
Department	UCL Ear Institute
Institution	UCL

DEVELOPMENTAL PATHWAY FUNDING SCHEME: MILESTONE FORM

Section 6: Deliverability – Project Plan

Please provide a GANTT chart of the proposed plan showing:

- project tasks (these being short, achievable and measurable activities) with, where relevant, the party responsible for delivering the task and dependency relationships between tasks and
- typically two to three progression milestones (to include the project end goal) these being major specifically-timed decision points when a judgment will be made on whether or not to progress the project based on the achievement/non-attainment of specific measurable targets

The GANTT chart must be converted to a pdf file and submitted via EAA as part of your full application for DPFS funding via the case for support page. Please name this your GANTT File *[Your Application ID] - GANTT*

Please complete the following project milestone data sheets for each of the two to three progression milestones (to include the project end goal). Please note that

- Milestones must be SMART that is Specific, Measurable, Achievable, Relevant, and Time framed
- The success criteria are the key measures that must be met in order for the project to be considered a success to that point thereby justifying progression
- **For each success criterion, please specify a quantified target value that you will seek to attain and a quantified acceptable value, which, if achieved, would support project progression**
- DO NOT include project management meetings or other process-related tasks as milestone
- Your estimate of the milestone criteria being met should assume that the preceding milestone was achieved

DEVELOPMENTAL PATHWAY FUNDING SCHEME: MILESTONE FORM

Section 6: Deliverability – Project Plan (M1)

Milestone 1 (M1)	
Time from Start to M1 (months)	13
Expenditure from Start to M1 (£000s)	1014
Estimate of meeting M1 criteria (%)	95

M1 Objectives (max 250 words)

1. The aim of this milestone is to start a clinical trial of a stem-cell based tissue engineered partial laryngeal replacement.

Objectives are:

a. Obtain necessary permissions by 8 months. These are Clinical Trials Authorisation from MHRA, Research Ethics Committee and NHS Research & Development permissions.

b. Recruit first patient by 12 months.

c. Implant the first patient by 13 months.

M1 Success Criteria and Target Values (max 250 words)

a. Success in obtaining Clinical Trials Authorisation from MHRA, Research Ethics Committee and NHS Research & Development permissions are requirements for the commencement of a clinical trial. They are yes/no values that have to be passed. We aim to complete these within 8 months, and we set an acceptable target of 10 months.

b. We aim to recruit our first patient to our clinical trial by 12 months.

c. We aim to have implanted this patient by 13 months, but 14 months would be acceptable.

M1 Justification for Criteria and Values (max 250 words)

a. We already have advanced, clinically-tested protocols and SOPs with most of the data required for a PSF. Our GMP delivery team are highly experienced in applying for CTAs for ATMP trials. We have engaged in frequent, face-to-face dialogue with the MHRA and have targeted the required work to fit their expectations and recommendations accurately. Our CTU provides all necessary personnel and environment to deliver successful REC and R&D approvals on time, with a wealth of clinical trial experience behind them. Eight months is an entirely realistic time-point for successful completion of these tasks, but in the event of unexpectedly lengthy correspondence with one or more of these organisations, we set an acceptable target of 10 months. We do not expect such slippage to affect overall project length.

b. We do not expect any slippage with this, as we have willing, eligible candidates for the trial already identified and the main barriers to recruitment are the obtaining of permissions as above.

c. We have had the opportunity to 'field test' our production and clinical processes so have mimimised the chances of failure or slippage in implantation of the construct. Normally, it would take us one month to produce a customised implant and this is our target here. However, as this is the first laryngeal patient to be implanted, we set an acceptable interval between recruitment and implantation of two months, hence the 14 month acceptable limit. This one month slippage would be discussed with MRC and no-cost extension proposed.

DEVELOPMENTAL PATHWAY FUNDING SCHEME: MILESTONE FORM

Section 6: Deliverability – Project Plan (M2)

Milestone 2 (M2)	
Time from M1 to M2 (months)	7
Time from Start to M2 (months)	20
Expenditure from M1 to M2 (£000s)	678
Expenditure from Start to M2 (£000s)	1692
Estimate of meeting M2 criteria, if M1 achieved (%)	85

M2 Objectives (max 250 words)

The aim of this milestone is to recruit adequately in a timely manner, since failure to do so is one of the main reasons for failure of trials, especially those involving surgery. We add a laboratory-based outcome also. Thus, our objectives are:

a. Recruitment of 5 patients
b. Completion of recruitment
c. Submission of manufacturing procedures for assessment of IP

M2 Success Criteria and Target Values (max 250 words)

a. The recruitment of 5 patients by 16 months will be measured by the signing of our trial patient consent form by at least five eligible recruits. We set an acceptable limit of 20 months.
b. The recruitment of our target of ten patients will be measured in the same way, with a target of 20 months, but an acceptable limit of 24 months.
c. Detailed, validated manufacturing protocols for all production steps will be submitted to UCLB for assessment of any IP which can be protected by 18 months, but an accetable limit of 20 months.

M2 Justification for Criteria and Values (max 250 words)

We have already identified four eligible and willing patients for this trial, so have a 'flying start'. Recruitment will be maximised by engagement with professional (British Association of Laryngologists) and patient (Ourairaway.com) bodies, and by qualitative methodology. Given the known presentation rates of these patients to the London Airway Service (see main form), we are confident that both of these targets are realistic. However, we are aware of the complexities of surgical trials and therefore set an *overall* acceptable limit for recruitment of 24 months (i.e. total recruitment period 12 months, but with a target of 8). Any such slippage will be discussed with the MRC and a no-cost extension requested to accommodate the lengthened follow-up time. The assessment of possible IP generated by our product manufacturing process is key to maximising commercial potential, and requires our laboratory staff to prepare detailed advanced protocols, including details of any devices such as bioreactors and delivery systems, developed by our team. UCL Business (UCLB) will then assess the potential for protection of such IP. This step is placed relatively early in the project in order to reduce the risks from competitors, real and potential.

improve processes. The considerable 'learn-by-doing' during product preparation/implantation will lead onto the development of refined SOPs and clinical procedures in preparation for commercialisation, for which cost containment is critical. Hence, this milestone is set one year after the expected completion of implantation.

DEVELOPMENTAL PATHWAY FUNDING SCHEME: MILESTONE FORM

Section 6: Deliverability – Project Plan (M3)

Milestone 3 (M3) [if applicable]	
Time from M2 to M3 (months)	12
Time from Start to M3 (months)	32
Expenditure from M2 to M3 (£000s)	758
Expenditure from Start to M3 (£000s)	2450
Estimate of meeting M3 criteria, if M2 achieved (%)	90

M3 Objectives (max 250 words)

This milestone revolves around clinical efficacy and process efficiency. We aim to demonstrate clinical efficacy at 6 and 12-month points post-implantation using clinically important measures, whilst achieving important increases in process efficiency and thereby cost-reduction. Thus, objectives are:

a. Two patients clinically successful 6-months post-implantation
b. Two patients clinically successful 12 months post-implantation
c. Significant process cost reduction

M3 Success Criteria and Target Values (max 250 words)

a. : For this sub-milestone, our target is 22 months, but a limit of 24 months is acceptable. Clinical success at the 6-month post-implant point is defined by the achievement by individual patients of three out the following five criteria:

1. Freedom from tracheostomy (yes/no)
2. Freedom from stent (yes/no)
3. Narrowest part of airway >80% normal on CT scanning. (Myer-Cotton grade1 equivalent, acceptable target 70%)
4. Respiratory performance of >80% predicted peak expiratory flow rate (PEFR) on pulmonary function testing (acceptable target is 65%)
5. No anti-donor antibodies detected in serum samples (yes/no)

b.: Clinical success at the 12 month post-implant point is defined using the same criteria as for the 6-month point. For this sub-milestone, our target is 30 months, but a limit of 32 months is acceptable.

c. For the third sub-milestone, our target is 32 months, but a limit of 34 months is acceptable. Significant process cost reduction is defined by achievement of 2 out of 3 of the following:

i. Reduction in laboratory production costs by 33% compared to baseline calculations included in the grant (acceptable 25%).
ii. Reduction in surgical implantation costs by 25% compared to baseline calculations included in the grant (acceptable 15%).
iii. Reduction in costs of follow-up by 30% compared to baseline calculations included in the grant (acceptable 20%).

M3 Justification for Criteria and Values (max 250 words)

Although we set a 12-months' follow-up point as the key clinical milestone by which to measure efficacy, our published data shows that 95% of patients undergoing complex airway reconstruction who reach the 6 month point go on to achieve long-term clinical success (Nouraei, 2007). Thus, we here include both 6-month and 12-month marks herein. The presence of a prosthesis-free airway is our principal outcome measure, and is represented by two criteria here. However, quantitation of airway diameter, and peak expiratory flow rates are also clinically important guides. We wish to be reassured of the absence of a rejection response to the donor scaffold, hence measure 5. 13 of 16 (81%) of pigs in our preclinical trials achieved clear airways at censor point (equivalent to one year in human terms). However, subsequent technical refinements have addressed the likely causes of failure, and in man we have interventions to maintain life and airway which are not permitted in Home Office regulated animal studies. Therefore, the 90% estimate for meeting this milestone is realistic. Nonetheless, to anticipate unexpected delays, we set an acceptable limit of 34 months overall. In this case, we will discuss with MRC and request no-cost extension. Sub-milestone (c) is achieved by applying Total Quality Management to continuously

DEVELOPMENTAL PATHWAY FUNDING SCHEME: MILESTONE FORM

Section 6: Deliverability – Project Plan (M4)

Milestone 4 (M4) [if applicable]	
Time from M3 to M4 (months)	18
Time from Start to M4 (months)	50
Expenditure from M3 to M4 (£000s)	1094
Expenditure from Start to M4 (£000s)	3544
Estimate of meeting M4 criteria, if M3 achieved (%)	95

M4 Objectives (max 250 words)

The aim of this milestone is to achieve all major reports required at the project's end. Thus, our objectives are:

a. Completion of follow-up
b. Reporting to MRC
c. Main paper accepted for publication in high impact peer-reviewed journal
d. Reporting to MHRA of trial closure

M4 Success Criteria and Target Values (max 250 words)

a.: We will complete 24 months' follow-up on ten patients by 44 months (46 acceptable)
b.: We will produce a detailed final report to MRC by 50 months
c.: We will produce a paper describing the trial and its outcomes and submit this for publication in an appropriately focussed high-impact journal, here defined as one with an impact factor >12 (>8 acceptable). Target for acceptance is 50 months, but 56 months is acceptable and incurs no additional cost.
c.: We will reporting to MHRA of trial closure by 50 months. However, in our experience, this process can occasionally take significantly longer than anticipated. Therefore, an acceptable value of 56 months is set, at no additional cost.

M4 Justification for Criteria and Values (max 250 words)

MHRA recommended 24 months' follow-up. However, for reasons presented in M2, M3, a cumulative slippage of 4 months is acceptable. In this case, a no cost extension will be discussed with MRC. Reporting to MRC is a requirement of funding and to MHRA is a requirement of the granting of a clinical trials authorisation (CTA). Even with slippage in M4a, since this is an open trial, a near-final report can be prepared as the last few patients near completion, so missing the M4b milestone is unlikely. The highest impact journals with appropriate reach for highly novel trial reports are the New England Journal of Medicine and the Lancet, and a scientific paper based on the trial will be submitted to one of these prior to the 50 month mark, with the expectation of acceptance by 56 months. We plan for a short turn-around since we have built adequate preparation time into the project. Since this is a high-profile advance of wide general scientific, clinical and public interest, and we have a strong track record of high level publication of our previous first-in-human studies, we do not feel it is over-ambitious to aim for this level of publication.

Birchall etal: RegenVOX. Figures and tables.

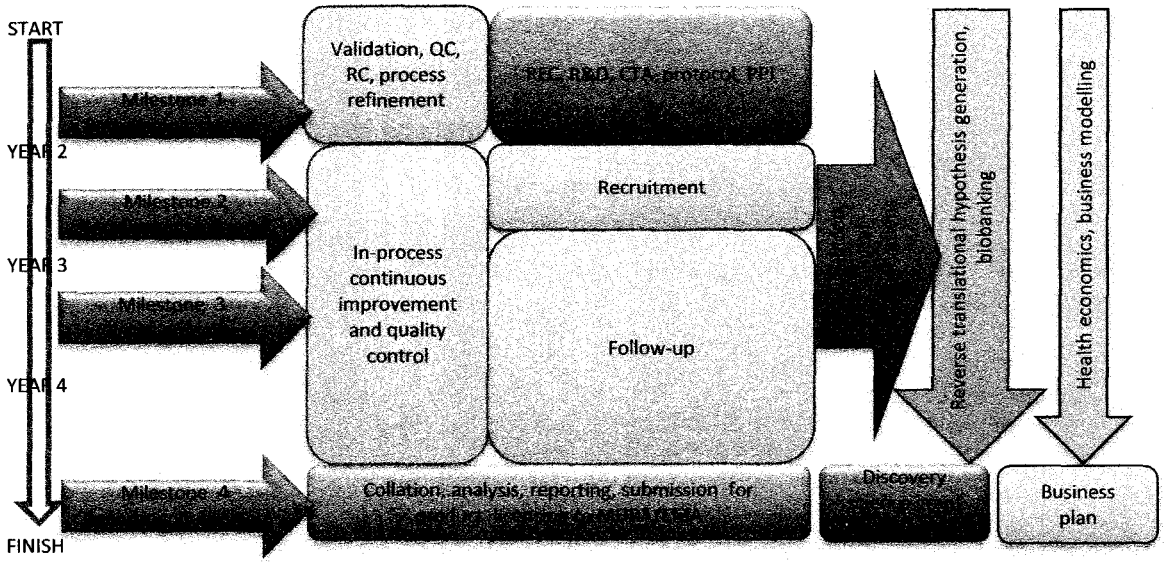


Figure 1. RegenVOX overall project flow-chart

Table 1. Schedule of Activities Phase I/II clinical trial

PROM = patient reported outcome measure; ADVS = airway, dyspnea, voice, swallowing index; PE= physical examination; PFT=pulmonary function test; CBC=complete blood count; V=visit; Adv=adverse.

Study Activity	Screening (V1) Within 14 days of enroll	Cell retrieval (V2) Day 0	Airway implant procedure Day 30 (+/- 4 days)	Wk 1	Month 1 visit (V3) (+/- 7)	Month 2 visit (V4) (+/- 7)	Month 4 phone call (+/- 7)	Month 6 visit (V 5) (+/- 7)	Month 8 phone call (+/- 7)	Month 12 visit (V6) (+/- 7)	Month 15 phone call (+/- 7)	Month 18 visit (V7) (+/- 7)	Month 21 phone call (+/- 7)	Month 24 visit (V8) (+/- 7)
Consent	X													
Incl/Excl	X													
Med History	X													
Demographic	X													
Vital signs	X	X	X		X	X		X		X		X		X
Physical (PE)	X	X	X											
Brief PE					X	X		X		X		X		X
PFTs	X				X	X		X		X		X		X
CT Scan	X							X		X		X		X
Videostroboscopy	X				X			X		X		X		X
Questionnaires (Ped airway PROM / ADVS[1]; resource use		X			X	X		X		X		X		X
Max/min diameter (CT, endosc)	X	X			X			X		X		X		X
Blood work (CBC, serum chem, HLA, leuk subsets, cytokines)	X				X			X		X		X		X
Blood work (donor ab)	X							X		X		X		X
Bronchoscopy		X		X	X			X		X		X		X
Brushings			X	X	X			X		X		X		X
Marrow / airway biopsy		X												
Implantation			X											
Adv events					X					X		X		X
Medication	X	X		X	X	X	X	X	X	X	X	X	X	X
Adv events		X		X	X	X	X	X	X	X	X	X	X	X

Figure 2. RegenVOX manufacturing flow-chart

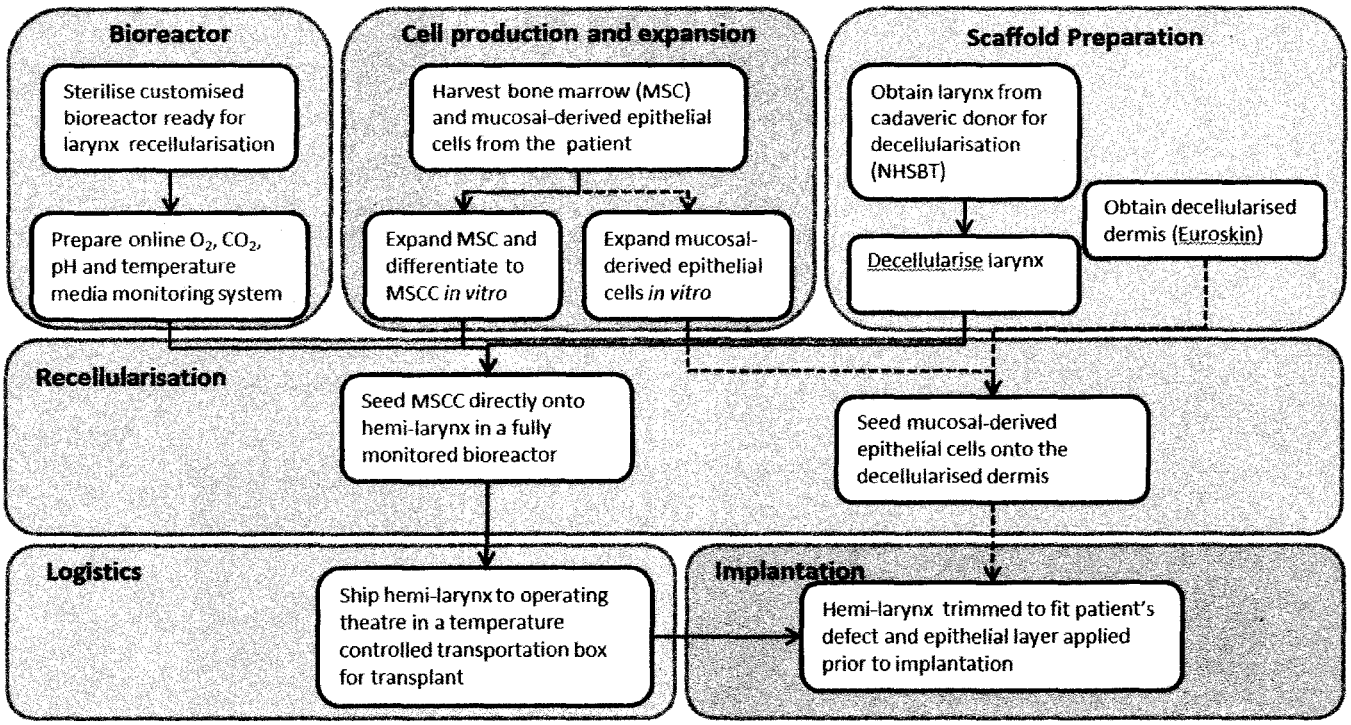


Figure 3. RegenVOX project management organisation chart

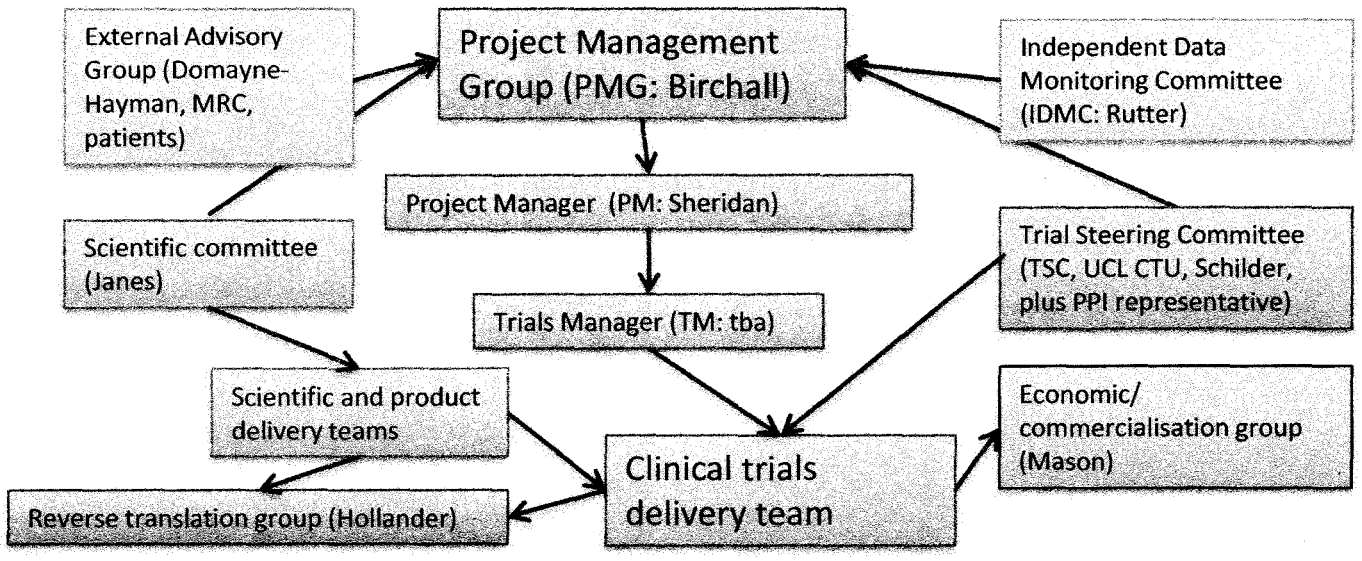


Figure 4a. Air-liquid interphase culture of primary bronchial epithelial cells at 3 weeks. A: H&E staining shows the formation of cilia (arrow). B: Functional goblet cells producing mucin shown by fluorescent immunocytochemistry (MUC5 staining-40x). C: Trans-epithelial resistance in air-liquid interface primary culture of bronchial and nasal epithelial cells showing greater barrier with cells of bronchial origin.

Figure 4b. (left) Decellularised larynx 24 hours post-seeding with primary human bronchial epithelial cells (H&E, 100X).

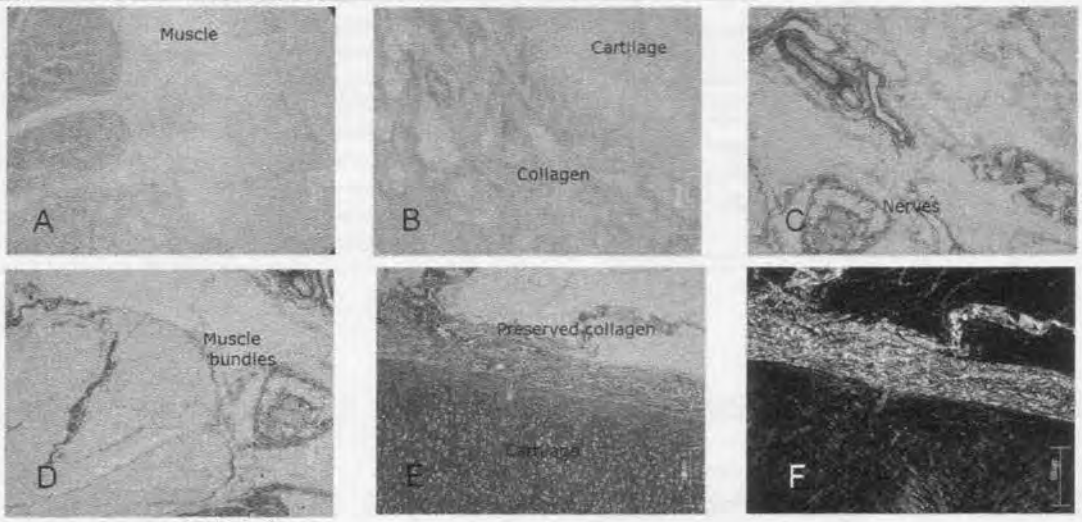


Figure 5. (above) Histological evaluation of the laryngeal scaffold following de-cellularisation using our protocol. A. De-cellularised porcine larynx stained with H&E; B. At higher magnification on a H&E stained sections no nuclear material is seen in either the cartilage or overlying muscle; C. A Picro S-Millers elastin stain shows excellent preservation of fine elastin; D. De-cellularisation also preserves fine collagen between muscle bundles; E. Thicker collagen over lying cartilage is well preserved; F. When viewed under there is good preservation of thick collagen (type 1) and collagen within the cartilage (type II).

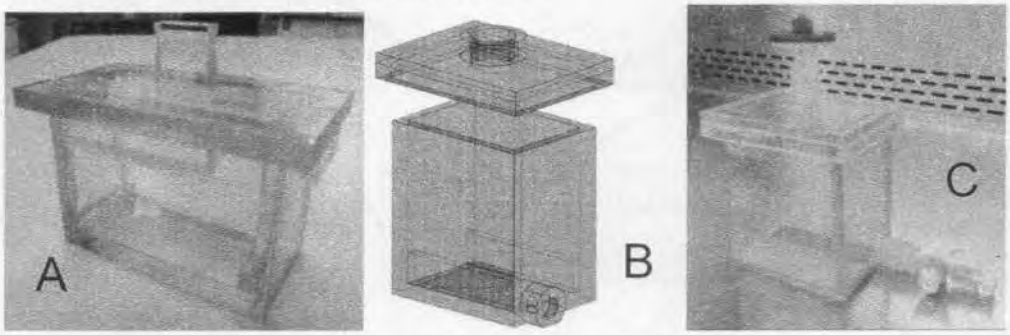


Figure 6. A: Prototype bioreactor successfully used to prepare grafts for GLP pig studies; B: AutoCAD design of version 2, reducing infection risk via continuous rim to lid and 2 added ports for media exchange and gas exchange respectively; C: the manufactured bioreactor for clinical use, with added O-ring seal and lid clamp.

Figure 7. GLP preclinical data

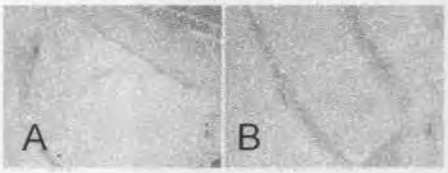


Figure 7a. A,B Two explanted grafts following biocompatibility studies in Sprague-Dawley rats one month after subcutaneous implantation. These showed decellularised material, with low inflammatory response and preservation of architecture, and integration with surrounding tissue.

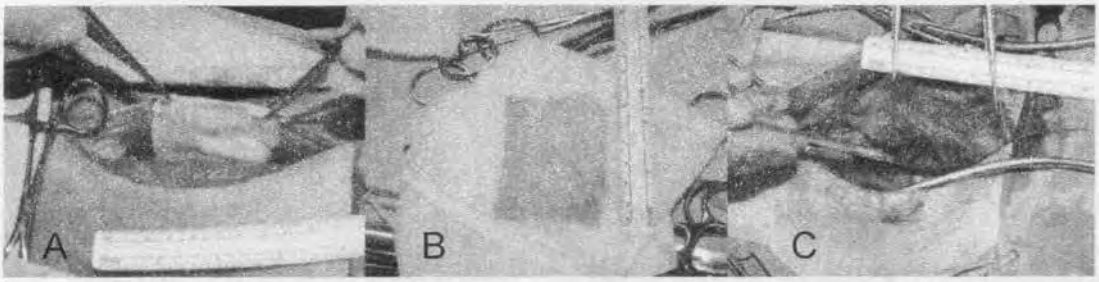


Figure 7b. A: Decellularised donor porcine hemilarynx scaffold seeded with human MSCC is implanted in a sternomastoid muscle pocket; B: tissue engineered mucosal graft consists of human mucosal epithelial cells grown on commercially available decellularised human donor dermis; C: mucosa is sewn onto internal surface of the graft which is then rotated into the laryngeal defect.

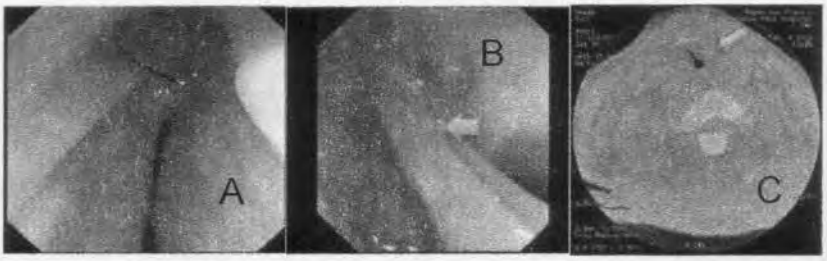


Figure 7c. A,B: Endoscopic images of implanted larynxes in pigs. In all cases, by one month, mucosal continuity was restored and a strong vocal cord profile seen by two months. C: CT scan of pig four months following implantation with a biologic scaffold. Due to difficulties in centring a pig within the scanner, the larynx appears rotated. However, the symmetry of the vocal cords and patency of the laryngeal airway can be clearly seen (arrow).

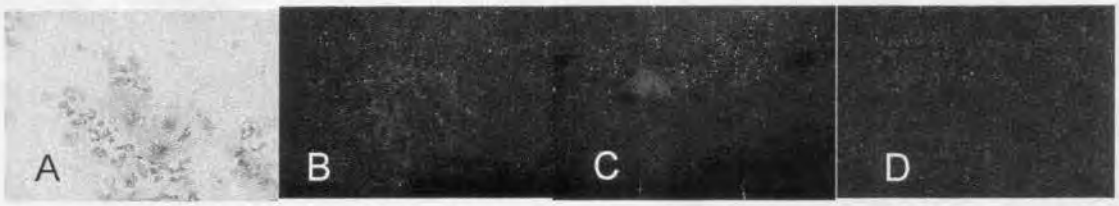
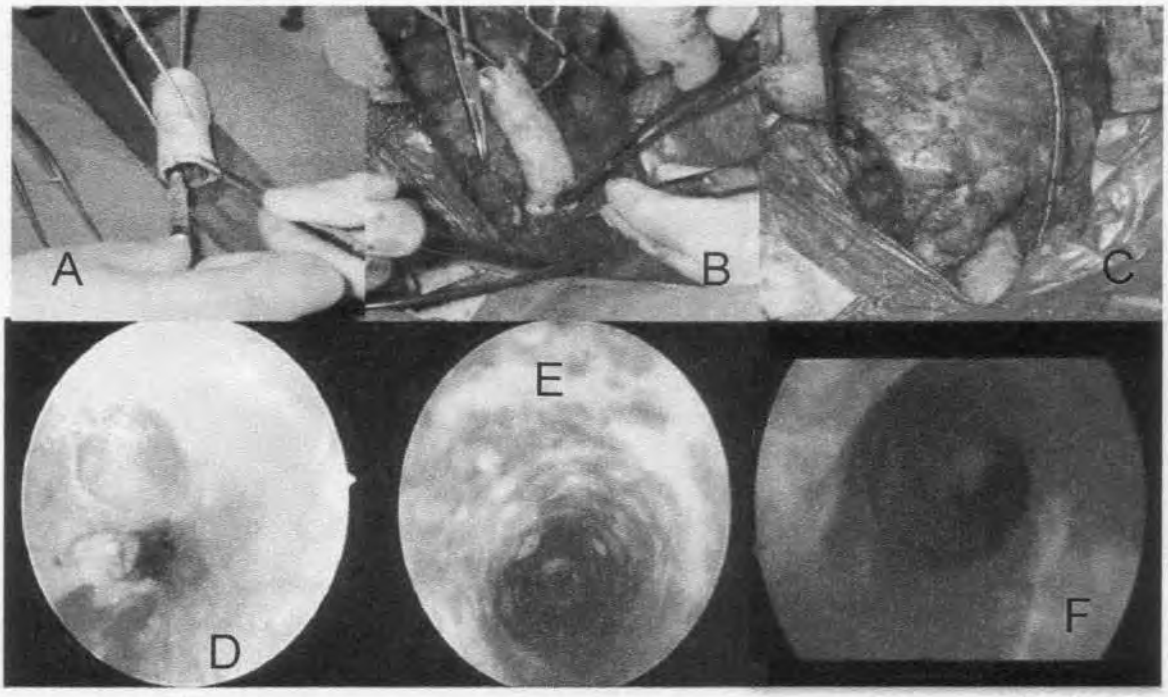


Figure 7d. Cytology of brushings taken from grafts at 2 weeks post-implantation. A: Viable epithelial cells populate the surface of grafts (H&E). B: On immunohistochemistry, viable human cells (red) can still be observed at two weeks (blue=nuclei, DAPI; green=Pancytokeratin; red = Cytokeratin 14, CK14) and C. at 4 weeks. D: control for species specificity shows no CK14 staining.

Figure 7e. Decellularised implant at two months. Complete tissue integration is seen (left) with extensively remodelled cartilage (right).



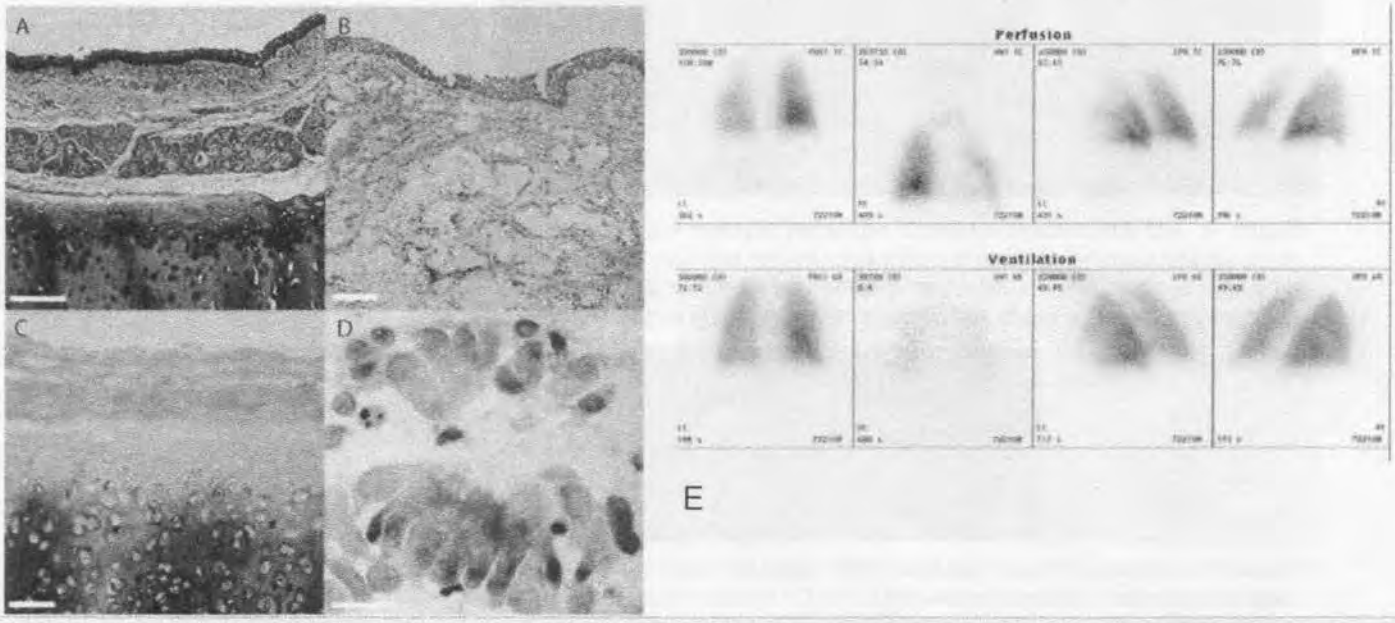


Figure 8 (upper panels). Compassionate use of a trachea prepared using prototype methods to those in present application. A. Graft being prepared for implantation; B. Implantation into the tracheal defect; C. Use of an omental wrap to cover the graft ; D. Microlaryngobronchoscopy 15 days following the transplant showed dense secretions; E. At 6 months airway is patent; F. Graft was still patent at one year, with healthy mucosa .

Figure 8 (lower panels). Haematoxylin and eosin staining of normal trachea (A) compared to the patient's previous tracheal homograft removed at the time of surgery (B) demonstrating an epithelialised lining but atypical gland formation. Sample of the decellularised tracheal graft employed here (C) showing loss of cells but preservation of normal architecture. Bronchial brushing (D) taken mid graft 1 year after surgery showed a cluster of ciliated cells. (Scale bars 250, 100, 100 and 20 μm respectively). E. A Lung Scan (V/Q) at eighteen months showed normal bilateral ventilation (the left lung is contributing 45% to the total ventilation and right lung 55%). This child is well, at school and growing 30 months post-implantation.

Medical Research Council

Additional Costs Proforma: NHS Support and Treatment Costs

MRC NHS Additional costs Proforma Version 1.1 15/11/2012

Supporting Data
NHS Costs form

Information

This form is used to clarify costs you are requesting from the NHS and the Department of Health (DoH) as part of your application for MRC funding. Any funds you wish to receive from the NHS or DoH should be entered on this form and **not** in the Resources or Costs section of your Je-S application. **Entering NHS costs in these sections of your Je-S application could invalidate your proposal.**

Justification for the costs detailed in this form must be clearly provided in your **Justification of Resources** document. Please also note that any award from the MRC will not include NHS Support costs or NHS Excess Treatment Costs/Savings. These will be paid directly from the NHS/DoH.

In addition to the MRC guidance, applicants should also read the document HSG(97)32, the DoH ARCO document and other Department of Health guidance on attributing the costs of non-commercial research that can be found on the DoH website.

Section 1: NHS costs in context

This section is designed as a form cover-sheet for reviewers and may be completed after the subsequent sections.

1.1 Please state the value of funding you are seeking from each source at 100% FEC.

MRC Research costs £	3544791
NHS Costs £	432160
Total Value £	3976951

Section 2: NHS Support Costs

2.1 Please complete the following table

Description of expected additional procedures/resource requirements	Cost per patient	Year 1 £	Year 2 £	Year 3 £	Year 4 £	Year 5 £	Overall Total £
Consenting	60	300	300	0	0	0	600
Questionnaires (PED/ADVS)	105	3706	3176	3176	0	0	10058
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
Total NHS Support Costs	**165**	**4006**	**3476**	**3176**	**0**	**0**	**10658**

2.2 Have you discussed these costs with the relevant MRC Programme Manager (PM)? Yes

2.3 If you answered 'Yes' to 2.2, please give the PM's name: Dr Foulkes

2.4 Please give the date of correspondence: 15/11/2012

2.5 Have you discussed these costs with your proposed NHS funding partner? Yes

Section 3: Estimated Treatment costs

Provide an estimate of the treatment costs involved in the research (and which would continue assuming that the patient care service in question continued after the research activity has stopped), along with the costs of the usual standard treatment of the condition. These costs should be determined in conjunction with your NHS Trust partner(s) and their commissioners

3.1 Please complete the following table

Description of expected resources required or released	Cost per patient	Year 1 £	Year 2 £	Year 3 £	Year 4 £	Year 5 £	Overall Total £
Videostroboscopy	380	7613	7612	7612	0	0	22837
Recist & PFT & Vital Signs	1922	70900	46062	46062	0	0	163024
VQ scan	450	4509	9016	9016	0	0	22541
Pathology (CBC; serum chem; leukocytes;	478	9560	9560	9560	0	0	28680
Bronchoscopy	3045	62620	60900	60900	0	0	184420
Total NHS Treatment Costs	**6275**	**155202**	**133150**	**133150**	**0**	**0**	**421502**

3.2 Is the patient care being provided different from the usual standard treatment for the condition? No

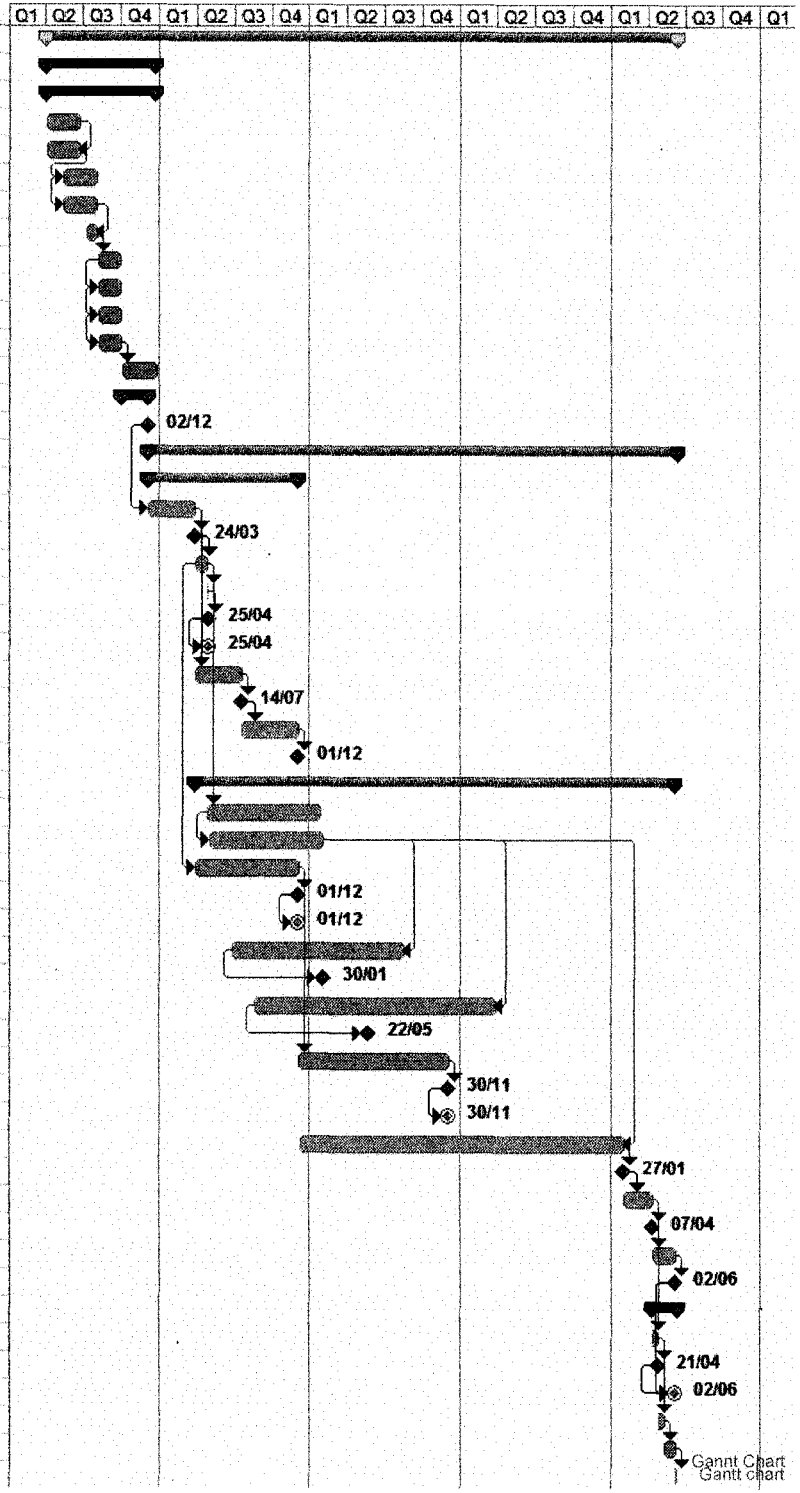
If you answered 'Yes' to 3.2 please complete Section 4: Estimated Treatment costs (continued).

Section 4: Estimated Treatment costs (continued)

4.1 Please complete the following table only if you have answered 'Yes' to 3.2.

Usual Treatment Costs Description of expected resources required or released	Cost per patient	Year 1 £	Year 2 £	Year 3 £	Year 4 £	Year 5 £	Overall Total £
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
Total NHS Unusual Treatment Costs	**0**	**0**	**0**	**0**	**0**	**0**	**0**

0	**RegenVox2 (Birchall)**
1	**Clinical Trial Preparation & 1st Participant**
2	**Regulatory and ethical approval**
3	Protocols development
4	Supporting document preparation
5	SOP preparation
6	CRF & Database design
7	Preparation of IRAS forms (MHRA, REC, NHS forms)
8	REC application process
9	NHS application process
10	MHRA application process
11	CLRN adoption
12	CLRN funding
13	**Site initiation**
22	**MS1a: Regulatory & local approvals obtained**
23	**Phase II Clinical Trial**
24	**Recruitment**
25	1st Participant recruitment
26	**MS1b: 1st Participant recruited**
27	Graft preparation
28	1st Participant implant
29	**MS1c: 1st Participant implant**
30	**Milestone 1: Clinical trial initiated and 1st Participant implant**
31	Participants 2-5 recruited
32	**MS2a: First 5 Participants recruited**
33	Participants 6-10 recruited
34	**MS2b: Recruitment complete**
35	**Implantation & Follow-up**
36	Graft preparation
37	Implantation
38	Refinement of Manufacturing Protocols
39	**MS2c: IP review of protocols**
40	**Milestone 2: Recruitment complete; Manufacturing protocols refined**
41	Follow-up 6 months
42	**MS3a: Clinical success 6 months post-implant (n=2)**
43	Follow-up 12 months
44	**MS3b: Clinical success 12 months post-implant (n=2)**
45	Process cost review
46	**MS3c: Process cost reduction**
47	**Milestone 3: interim clinical success; Cost reduction**
48	Follow-up 24 months
49	**MS4a: Trial complete**
50	Analysis, Final Report
51	**MS4b: Reporting complete**
52	Manuscript Prep & Submission
53	**MS4c:Manuscript Accepted**
54	**Trials closure**
55	TC reviews trial end reports
56	**MS4d: Closure reported to MHRA**
57	**Milestone 4: Trial successfully completed & reported; Project End**
58	TC submits forms to REC and MHRA
59	Confirmation letters received
60	Closeout procedures undertaken



TEMPLATE FOR A DATA MANAGEMENT PLAN

0. Proposal name

RegenVOX2: phase I/II clinical trial of stem cell based tissue engineered laryngeal implants

1. Description of the data

1.1 Type of study

This is a three-year project to encompass a phase I/IIa clinical trial of customized stem cell based laryngeal implants in ten adult patients with severe laryngeal stenosis who have exhausted conventional therapeutic options, and with two years' follow-up.

1.2 Types of data

a. *Clinical trial outcome data:* clinical measures; patient-reported outcome measures (qualitative and semi-quantitative); manipulated data: excel or equivalent
b. *Source data*: quantitative (temperature, blood pressure, EEG);
c. *Administrative: Standard operating procedures (SOPs) & Clinical Trial Protocol for the conduct and management of the trial compliant with UK regulatory requirements;* Standard operating procedures (SOP), protocols and a product specification file (PSF) for submission to MHRA
d. *Imaging data* CT (6, 12 & 24 months)
e. *Tissue samples:* Airway brushings and blood samples will be used for 'reverse translation' development of hypotheses regarding mechanisms.

1.3 Format and scale of the data

a. Clinical trial outcome data: Ten patients with data collected at seven data points over a two year period *recorded on trial specific case report forms (CRFs) and uploaded to a dedicated trials database (MACRO 4) compliant with national regulatory requirements and held securely by the UCL CTU. The CRFs will be securely stored at the clinical site.*
b. *Imaging data CT (6, 12 & 24 months) raw data: DICOM (Digital Imaging and Communications in Medicine) standards to store images; extracted data: excel or equivalent, statistical data package e.g. R and MATLAB*
c. Raw data: paper records and/or standard non-proprietary formats;
d. SOPs and PSF will be delivered in the standard hard and electronic copy forms required by the MHRA.
e. Blood and cytology samples will be stored in the UCL/RFH Biobank at the Royal Free Hospital (HTA licence 11016; DI – Dr Mark Lowdell). Data pertaining to each sample will be stored in accordance with HTA regulations using established GCP-compliant procedures.

2. Data collection / generation

2.1 Methodologies for data collection / generation

The trial is subject to Research Ethics Committee (REC) approval and will comply fully with the UK Data Protection Act 1998 and the UCL requirements relating to patient confidentiality.
Patient-specific data will be collected by our dedicated research nurse following written informed consent from the trial participant and subsequently entered remotely at site onto a secure trial database. This is managed in accordance with the Data Protection Act.
A proportion of data recorded will be checked at site using source data verification. All data will be centrally monitored using a variety of methodologies including visual checks, range and validation checks
Principal outcome by clinical observation.
Secondary outcome measures: i) Safety by clinical observation; development of anti-donor antibodies will be measured by blood assays; ii) Efficacy: by clinical observation; iii) Symptoms/quality of life (SF36): Resource use are all measured by self-completion questionnaires. Health system resource use measured by questionnaire applied by the research nurse to the health system (GP, hospital, pharmacies).

2.2 Data quality and standards

5. Selected publications

Vallejo-Torres L, Morris S. (2012). Income-related inequity in health care utilisation among individuals with cardiovascular disease in England – accounting for vertical inequity. Health Economics (forthcoming).

Christensen M, Morris S, Vallejo-Torres L, Vincent C, Mayer SA. (2011). Neurological impairment among survivors of intracerebral hemorrhage: The FAST trial. Neurocritical Care (forthcoming).

Christensen M, Morris S, Banner C, Lefering R, Vallejo-Torres L, Boullion B. (2011). Quality of Life after Severe Trauma: Results of the Global Recombinant Factor VII Trauma Trial. Journal of Trauma, vol 70(6):1524-31

Vallejo-Torres L, Steuten L, Parkinson B, Girling A, Buxton M. (2010). Integrating Health Economics into the product development cycle: the case study of absorbable pins. Medical Decision Making, vol 31(4):596-610

Vallejo-Torres L, Morris S. (2010). The contribution of smoking and obesity to income-related inequalities in health in England. Social Science and Medicine, vol 71(6):1189-1198

Vallejo-Torres L, Morris S. (2010). Factors associated with the use of primary care services: the role of practice nurses. European Journal of Health Economics, vol 12(4):373-81

Steiner T, Vincent C, Morris S, Davis S, Vallejo-Torres L, Christensen MC. (2010). Neurosurgical Outcomes After Intracerebral Hemorrhage: Results of the Factor Seven for Acute Hemorrhagic Stroke Trial (FAST). Journal of Stroke and Cerebrovascular Diseases, vol 20(4):287-94

Vallejo-Torres L, Morris S, Carr-Hill R, Dixon P, Law M, Rice N, Sutton M. (2009). Can regional resource shares be based only on prevalence data? An empirical investigation of the proportionality assumption. Social Science and Medicine, vol 69(11):1634-42

Steuten L, Vallejo-Torres L, Bastide P, Buxton M. (2009). Analysing uncertainty around costs of innovative medical technologies: The case of fibrin sealant (QUIXIL ®) for total knee replacement, Health Policy, vol 89(1):46-57

Vallejo-Torres L, Steuten L, Buxton M, Girling AJ, Lilford RJ, Young T. (2008). Integrating health economics modelling in the product development cycle of medical devices: a Bayesian approach. International Journal of Technological Assessment in Health Care, vol 24 (4):459-64

Steuten L, Vallejo-Torres L, Young T, Buxton M. (2008). Transferability of economic evaluations of medical technologies: a new technology for orthopedic surgery. Expert Review of Medical Devices, vol 5, no 3:329-36

Overview: This is a substantial project that brings a complex cell-based ATMP from bench to bedside. Although we have performed a significant amount of preparatory work, laboratory and CTU work remains to obtain all necessary permissions and have the production processes fine-tuned for the start of the trial at the end of year one. This product requires parallel teams to deal with cell, tissue and bioreactor parts of production, and prepare for and run a clinical trial.

Laboratories for Cellular Therapeutics: This is the site of most of the implant production processes. The aspects of the project under the direction of Dr Lowdell (DA salary costs) relate to the final GMP translation, the generation of the investigational medicinal product dossier for submission as part of the CTA and then the GMP manufacture of the products for clinical trial. These costs are incurred only during the first three years of the project and are assigned as such. The bulk of the costs are, inevitably, staff costs and include a single full-time and one part time research scientist plus a part-time administrator to support the entire project team. The named full time scientist, Carvalho, is an existing staff member who has developed considerable experience in GMP manufacture and paperwork. She has been integral to the pre-clinical manufacture of the larynx for the porcine experiments but was also part of the team which made the first re-cellularised cadaveric donor trachea as an ATMP earlier this year. GMP scientists are rare and expensive to train so Ms Carvalho is an essential member of this programme with skills transferrable across many aspects. The named part-time scientist, Jide-Banwo, is part of Dr Lowdell's existing group and is trained in all of the relevant skills to support this project in manufacturing and trial sample management in the UCL/RFH Biobank. GMP manufacture requires a minimum of two operatives at all times to complete the contemporaneous manufacturing record. Carvalho will be the dedicated GMP lead for the project and Jide-Banwo will support her in the GMP processing. We will provide the remaining GMP support from existing staff resources within Dr Lowdell's group.

LCT consumables costs are calculated to provide products for GMP process engineering and GMP process validation in addition to the final GMP products for trial use. The requirement for process engineering and validation is an integral part of GMP manufacture and requires the use of the same GMP-compliant reagents and disposables as the final manufacture. Fully one third of these costs is the provision of cadaveric airways from NHSBT. The remaining costs of GMP manufacture relate to the access charges for use of the GMP manufacturing laboratories. These are charged at "cost" to cover the provision of the quality management staff (QM and QC personnel), regulatory authority licensing, the maintenance and calibration contracts for equipment and routine GMP disposables. The hospital overheads are stripped from these charges.

Centre for Respiratory Research: This is the site for epithelial cell preparation and science. Janes (DA salary costs) will oversee cell production, obtain bronchial biopsies and assist with patient care (bronchoscopy). We have applied for a post-doctoral research fellow for the epithelial component of the grant. This person will need extensive expertise in airway cell culture and differentiation, hence a relatively high spine point. They will work closely with Dr Janes in understanding what cells and what matrix interactions are required for cell growth. The average laboratory consumables cost for the Rayne building is £18,000 per year. However, the additional demands of GMP manufacture have raised this figure slightly, for example the current high price of the Human Bronchial Epithelial Cell culture medium.

UCL Ear Institute: This is the management hub and clinical base for the project. PI Birchall will supervise the project overall and participate in clinical activities, and one day per week (DA) is allocated to this. Sandhu (DA) is the principal clinician and will oversee patient care, perform operations and endoscopies and participate in trial management (with Birchall), hence half a day is requested. Schilder (DA) is clinical trial lead and requires two hours per week. Importantly, we require support for a clinical research fellow to recruit patients, organize clinical visits, investigations, endoscopy, consenting, follow-up and operating theatre sessions and to provide

clinical assistance for all of these. The clinical fellow will act as a focal point for patient contact and liaison and ensure communications between clinical and laboratory teams are effective. Funds for project management include the costs of a PM (Sheridan, DA) and support, recruitment, office consumables, meetings and travel costs (two conferences per annum, two staff each: ISSCR, TERMIS), laptop computer and software/upgrades for clinical research fellow to maintain databases and support research at multiple sites. An essential bioreactor control system is included in EI costs, quoted at 35,000, for which 22,500 is requested as per agreement with UCL. We require costs for PPI group engagement (meetings, travel, accommodation). The clinical costs over and above normal NHS care are also requested for patients enrolled, and include outpatient, investigation, patient travel and accommodation and inpatient/operating theatre costs, and short high dependency care stays. Some of these costs may have been incurred anyway, but in an unpredictable manner, and in distant institutions in many cases. Here, we standardise everything in an appropriately equipped and staffed, hospital at our clinical and scientific base, UCL/UCLH.
UCL CTU: We require funds for a clinical trials support team (relevant sessional time of manager, data manager, PPI officer, programmer, HE and statistical support) to prepare and submit materials for obtaining relevant permissions, prepare trial documentation, initiate, manage and monitor the clinical trial. This team will also perform data collation, management and statistical analysis and assist with reporting. Co-I Tebbs is costed in (DA) and joins the PMG and TSC.
Statistics: Costs are required for professional statistician and Co-I Dr Gareth Ambler (DA salary) to provide statistical support for this trial, which will include analysis and interpretation of the data.
Division of Surgery: Costs are requested for RA Darbyshire to produce and maintain bioreactors. Darbyshire will also perform total quality management for technical aspects of bioreactor refinement and production processes and be principal liaison for reverse translation supervised by Hollander. Co-I Seifalian (DA salary costs) will oversee bioreactor development and be part of the PMG. Costs of bioreactor construction, quality control and development are requested.
Regenerative Medicine Bioprocessing: We request funding for an engineer/economist to ensure that activity is kept on target to deliver a therapy that is both safe and clinically effective, and equally welcomed by the NHS for routine clinical practice. Many cell-based therapies have been developed at vast expense, but failed to prove clear cost:benefit advantage. To demonstrate such advantage requires an understanding of the whole pathway: the impact of changing one component on this ratio must be understood. We will develop alternate models to include NHS-embedded services, external commercialisation and combinations. To produce a transformative therapy that restores patient/carer quality of life and benefits the NHS by reducing resource-use requires robust analysis of cost of goods, healthcare, unemployment and societal implications. We will develop new methodologies for guiding the development of transformative therapies that replace a lifetime of frequent healthcare intervention and medication with a one-off cure. Whilst this work-package adds £0.5M herein, the final saving to the NHS/DH and Department Of Work and Pensions could, over the lifetime of the RegenVOX product, be orders of magnitude greater.
NPIMR: Co-applicant Ansari (DA) is responsible for continued optimisation/characterisation of de-cellularised larynx. As the technology to produce the scaffold matures, improvements can be incorporated immediately. This will require 10% of her time over the first 36 months of study.
University of Bristol: Hollander (DA) will horizon scan for discovery science opportunities. He will develop pathways to reverse translation for stem cell based ATMPs, which will be of generic benefit to regenerative science. He will be involved with experimental design, data analysis and prioritisation of downstream decisions. He will utilise extensive experience in stem cell research and his well-developed environment. He will develop links with the highest quality discovery science partners, for example those populating the MRC-funded Crick Institute near UCL.

UCL Business PLC
The Network Building
97 Tottenham Court Road
London W1T 4TP

T . +44 (0)20 7679 9000
F . +44 (0)20 7679 9838
W. www.uclb.com

MRC Developmental Pathway Funding Scheme

Our Ref: 20-021

12th November 2012

LETTER OF SUPPORT FOR THE DPFS PROPOSAL OF PROF MARTIN BIRCHALL

We wish to express the support of UCL Business PLC (UCLB) for the RegenVOX: Phase I/II clinical trails of stem cell based tissue engineered laryngeal implants project from Prof Birchall.

UCLB is delighted to be part of the excellent team assembled for this project. Prof Birchall was part of the team involved in the very first Laryngeal implant procedure using a polymer based organ scaffold (engineered at UCL) which was populated by autologous stem cells. Two subsequent procedures were successfully performed using a donor hollow organ seeded with stem cells for compassionate use. An MRC-TSCRC funded development programme is currently ongoing to perform the necessary development activities prior to initiation of the clinical trial – which is the subject of this funding application. The stem cell GMP manufacturing procedures developed at UCL/UCLH by Dr Lowdell and the clinical expertise of the Birchall team make this a very interesting research proposition which UCLB are very excited to be associated with.

UCLB has assigned an experienced Business Manager to oversee and manage the commercial and IP aspects of this project. The initial MRC-TSCRC funding study has not generated any new IP. Should new IP be developed during the initial phase of this follow on clinical trail then a patent application will be filed to cover said IP with a view to commercialising the technology at a later date.

UCLB has considerable resources available to support the development of this technology, including a Project Management team to work on prototyping and scale-up issues in manufacture, a Proof of Concept fund for new IP exemplification, and an outstanding IP/legal team to support patent prosecution and contract negotiation should it be required.

With Kind Regards

Rebecca Paulraj
Business Manager
UCLB

Anne Lane
Executive Director
UCLB