1. This submission from the Medical Research Council provides the additional information on these two issues requested by the Committee; on the current status of the MRC-funded grant RegenVOX, which was awarded through the Biomedical Catalyst (BMC) Development Pathway Funding Scheme; and on the MRC’s approach where a funded application has subsequently been found to have flaws.

MRC award RegenVOX: phase I/II clinical trial of stem cell based tissue engineered laryngeal implants, Professor Martin Birchall, University College London. £2,856,445 (Jun 13-Aug 18)

2. The MRC funded the RegenVOX\(^1\) study in 2012. The award started in June 2013 however the clinical trial proposed as part of the study is currently paused and no patients have yet been treated as part of the trial.

3. The current RegenVOX grant followed on from a previous MRC-funded grant held by Professor Birchall at UCL. The initial RegenVOX\(^2\) award started in 2011 and supported a laboratory-based study to underpin development of a ‘tissue-engineered larynx’ using both synthetic and biologic (cadaveric) scaffolds, including animal studies in pigs. The study demonstrated that synthetic scaffolds were inferior to biologic ones; since this finding synthetic scaffolds have not been pursued further with MRC funding.

4. In 2012 Martin Birchall applied to the MRC’s BMC: Developmental Pathway Funding Scheme (DPFS) for funding to conduct further pre-clinical testing and a clinical study of larynx replacement focused on the cadaveric implant. The BMC is a unique partnership between the MRC and Innovate UK, and the DPFS scheme is a key part of the MRC’s Translational Research Strategy, supporting the translation of fundamental discoveries toward benefits to human health. It funds the pre-clinical development and early clinical testing of novel therapeutics, devices and diagnostics, including “repurposing” of existing therapies. Projects supported by the scheme have clearly defined milestones, outcomes and future plans; these help to maximise both the chance of success and the likelihood of the project attracting the downstream funding, from public or private sources, required to meet its clinical and commercial aims.

5. The DPFS review process has two stages, involving written review by a range of experts followed by an interview with the Major Awards Committee\(^3\) where applicants are questioned about the project plan including the data underpinning their application. In reviewing the application from Professor Birchall and his team, the Committee judged that there was sufficient compelling evidence to justify further research to investigate whether a tissue-engineered larynx could be clinically beneficial, and awarded funding in a competitive process. The previous MRC-funded grant held by Professor Birchall involved a pig study undertaken to regulatory standards, the data compiled from this was used for a regulatory submission to the Medicines and Healthcare Products Regulatory Agency (MHRA) in the second award, followed by a clinical trial. As indicated above, all Biomedical Catalyst DPFS

\(^1\) http://gtr.rcuk.ac.uk/project/6039BD76-9195-433C-894E-4536CF2FCA74
\(^2\) RegenVOX. Stem-cell based, tissue engineered laryngeal replacement. Professor Martin Birchall, University College London, £1,153,543 (Apr 11-Aug 13): http://gtr.rcuk.ac.uk/projects?ref=G1001539
\(^3\) https://www.mrc.ac.uk/about/our-structure/research-boards-panels/bmc-major-awards-committee/
Written evidence submitted by the Medical Research Council (RES0032)

awards are milestone-driven and any significant modifications from the original research plan undergo further peer review.

6. At the time UCL started its inquiry into regenerative medicine earlier this year, the RegenVOX clinical trial proposal had received approvals from both the MHRA and the Research Ethics Committee (REC) but no patients had been treated. UCL decided to pause the RegenVOX trial until their inquiry was complete. Now that the UCL inquiry has reported, Professor Birchall will be able to make renewed submissions to both the MHRA and the REC which would consider all current information (including on patient safety) relevant to the trial. If appropriate approvals are obtained from both these bodies, Professor Birchall would need to submit a plan to the MRC (and UCL) outlining how they would complete the project taking into account any recommendations from the REC, MHRA etc., and MRC will seek further expert advice on the research plan.

7. Following the publication of the evidence submitted to the Committee from Professor Patricia Murray and Dr Raphael Lévy, the MRC’s Chief of Strategy has written to them, providing background on the MRC’s funding for the RegenVOX studies and responding to recommendations directed to the MRC. A copy of the letter is provided as Annex 1.

MRC approach where a funded application has subsequently been found to have flaws

8. In a situation where an MRC-funded study was later found to be based on an application that was flawed in some way, either as a result of honest error or proven research misconduct, the approach taken would depend on the stage at which the issue was raised with the MRC, who was found responsible for the issue and the extent to which the viability of the project was affected. For instance, the approach would differ depending on whether a concern was raised while the application was being assessed for funding, when a project was live or after a project had ended.

9. If a concern, or allegation of research misconduct, was raised during the assessment of an application, for example by an external peer reviewer or by a member of the funding Board or Panel, the MRC would raise the issue with the Research Integrity lead at the Research Organisation responsible for the application and ask them to investigate. The assessment of the proposal would be suspended while the issue was being examined. If the concerns were not founded, did not involve the investigators directly or were found to be an honest error, the MRC would likely continue the assessment, allowing the applicants to provide further information or resubmit the application as necessary. If the concerns were founded, the application would be rejected.

10. If an issue was raised while a study was ongoing or had ended, the MRC would ask the Research Organisation to investigate in line with any relevant policies, which may include research misconduct policies. Taking account of the extent to which the project was dependent on any data or information that was called into question, awards may be suspended while investigations are undertaken. In such cases the

---

http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/research-integrity/written/73987.html
Written evidence submitted by the Medical Research Council (RES0032)

Research Organisation would be expected to take appropriate steps to remove or minimise any risks that might result. Risks may relate to the health, safety and security of workers, research participants, or other persons, the welfare of animals or negative environmental consequences.

11. In all cases where research misconduct is proven, the MRC would consider sanctions depending on the severity of the case and having regard to the actions the Research Organisation has already taken. Sanctions may include the rejection of any applications under consideration on which the individuals concerned are named applicants or researchers, withdrawal of MRC funding, preventing any individuals concerned from submitting any further applications either for a specified period or indefinitely, and/or reclaiming any and all funding for projects involving the individuals. Should an unreported allegation of misconduct be discovered, the MRC may impose sanctions against the institution. Where any investigation finds a distortion or inaccuracy in the published research record, the institution should take all necessary steps to correct the public record.

December 2017
Dear Professor Murray and Dr Lévy,

MRC response to Professor Murray and Dr Levy

Patricia Murray
Professor in stem cell biology and regenerative medicine
Institute of Translational Medicine
University of Liverpool

Raphael Lévy
Senior Lecturer in nanotechnology and imaging
Institute of Integrative Biology
University of Liverpool

15 December 2017

MRC funding of work by Professor Martin Birchall (UCL)

We have noticed that your submission to the House of Commons Science and Technology Committee Research Integrity Inquiry, published on 21st November, contains references to MRC funding of work by Professor Martin Birchall of UCL. I am writing to provide background on those grants and the review process they have been through, together with additional responses to the parts of your submission and recommendations relevant to the MRC.

MRC Funding to RegenVox and Professor Birchall

It is important to be clear at the outset that, although the MRC has allocated funding for the RegenVox study, the clinical trial is currently paused and no patients have yet been treated as part of the trial.

In 2010, the MRC funded Professor Martin Birchall (G1001539/1 - RegenVOX. Stem-cell based, tissue engineered laryngeal replacement). This project was a laboratory-based study of different materials to underpin development of a ‘tissue-engineered larynx’; it included both synthetic and cadaveric larynxes seeded with stem cells. Plastic larynxes were placed in eight pigs and cadaveric larynxes in another eight pigs; this demonstrated that the cadaveric implants engrafted better. No subsequent development or testing of the plastic implants occurred with MRC funding. A further good laboratory practice (GLP) study, also supported by the MRC, of cadaveric implants in six pigs was designed to deliver safety data to the appropriate standard to satisfy the Medicines and Healthcare Regulatory Agency (MHRA). Data from pig experiments relevant to the RegenVox trial has been published.

In 2012 Martin Birchall applied to the MRC for funding to conduct further pre-clinical testing and a clinical study of larynx replacement focused on the cadaveric implant. This was considered through the MRC’s Biomedical Catalyst: Developmental Pathway Funding Scheme (DPFS). The review process was two-stage, with feedback from experts.

---

2 In vivo implantation of a tissue engineered stem cell seeded hemi-laryngeal replacement maintains airway, phonation and swallowing in pigs.
incorporated into the final ‘full’ application. The full application was reviewed by individuals with expertise across the relevant disciplines. The applicants then attended an interview with the committee, at which they presented further information and data and were cross-examined by the experts. In reviewing the application from Professor Birchall and his team, the committee judged that there was sufficient compelling evidence to justify research to investigate whether a tissue-engineered larynx could be clinically beneficial and awarded funding. All Biomedical Catalyst DPFS awards are milestone-driven and any significant modifications from the original research plan undergo further expert review.

At the point when UCL started their inquiry into regenerative medicine, approvals had been obtained from the MHRA and the Research Ethics Committee (REC) and one patient had agreed to join the RegenVox trial but the operation had not taken place. UCL decided to pause the trial until the outcome of the inquiry was known. Now that the inquiry has been published, new submissions to the REC and the MHRA are required. If these bodies approve re-starting the trial, the research team would need to submit a plan to the MRC (and UCL) outlining how they would complete the project taking into account any recommendations from the REC, MHRA etc., and MRC will seek further expert advice on the research plan.

Response to other points raised in the submission.

The initiation of the MRC’s increase in activity in the stem cells and regenerative medicine fields predated the first trachea implant operation on Claudia Castillo. The MRC’s decision to do this came about for several reasons. Scientifically, the stem cell research field had seen some interesting advances that showed promise; a number of examples could be cited, with the tissue engineering potential for tracheal/larynx replacement being only one that was covered widely in the press. At this time, the [Cooksey review](#) of UK health research funding had recently been published. This review led to the MRC receiving an uplift in funding from the UK Government to allow it to support more translational research, and stem cells was one area specifically highlighted in the report with potential. In 2007 the UK Government published its response to the [UK Stem Cell Initiative](#) report and recommendations. In this the Government specifically committed to supporting “Medical Research Council (MRC) initiative to support translational stem cell research and clinical trials”. Further significant investments in regenerative medicine have been made subsequently, such as the Regenerative Medicine Platform in 2012 through which you yourselves received funding.

The MRC agrees that we should ensure that any information that we provide is as accurate as possible, and we make every effort to do so. When new research funding or the outcomes of research are reported, an important component of contextualising the research for the benefit of stakeholders, including the public, is to outline the possible implications or benefits of the research. In your submission to the Inquiry, you cited a 2008 newspaper article, the 2011 MRC news story and the 2014-2019 MRC Strategic Plan as containing inaccurate information; all these were considered accurate at the time they were written based on the available evidence and information. Even where possible, the MRC does not retrospectively amend historic documents, but we accept that these might have been written differently in the light of what we know today. We do however think that the phrase ‘stem cell-engineered larynx’ could be considered an accurate description of the product involved in the RegenVox study– a de-cellularised larynx ‘seeded’ with stem cells.

The MRC’s primary role is to fund high quality research aimed at improving health; it is not a healthcare provider, nor a source of medical information. The MRC website has a page
entitled ‘Information for the Public/Stem cell therapy information’ which states “The MRC is unable to answer specific questions on whether stem cells can help with your specific condition; your GP or consultant is best placed to provide you with further advice.”.

The MRC does not state, and has not stated on its website, or in publications that “stem cells can make organs and tissues when injected into the body”. The MRC ‘Spotlight on: Regenerative Medicine’ does include an example of the potential for stem cells to restore eyesight in degenerative disease; however, this does not indicate that organs and tissues can be ‘made’ by injecting cells. It makes clear that this activity is at the research stage and that further investigation would be needed before any benefit to humans could be demonstrated. We are currently working on an update to the material on our web site on research into advanced therapies, including regenerative medicine.

In response to your recommendation “Government should solicit the views of a broad spectrum of experts, including those engaged in basic science, when deciding how best to allocate research funding, especially in the field of stem cells and regenerative medicine.” We agree entirely on the need for broadly based review and challenge in funding decisions on individual projects, and also in reviews of the productivity of broad fields of research. These funding decisions are made by MRC, rather than Government, though. Our decision-making panels routinely involve, at least, basic and applied research expertise and clinical practitioners, and often also industry R&D experts.

Declan Mulkeen
Chief of Strategy
Medical Research Council

cc    Rt Hon Norman Lamb MP, Chair, House of Commons Science and Technology Committee

https://www.mrc.ac.uk/research/initiatives/regenerative-medicine-stem-cells/information-for-the-public-stem-cell-therapy-information/