**Institution:** University College London

**Unit of Assessment:** 1 - Clinical Medicine

**Title of case study:** Introduction of percutaneous pulmonary valve implantation into clinical practice

## 1. Summary of the impact

Percutaneous heart valve implantation is an innovative, minimally invasive alternative to open-heart surgery for treating valvular heart disease. Over the last 10 years, research at UCL has advanced the original method of minimally invasive valve implantation in the pulmonary position. Over 5,000 patients have now benefitted from this procedure and have therefore avoided open-heart surgery. The research has been used for regulatory approval of the Melody™ device in Europe and Canada (CE marking) and has led to FDA approval in the USA for both the device and procedure and NICE approval in the UK.

## 2. Underpinning research

Dysfunction of the right ventricular outflow tract (RVOT) with pulmonary stenosis and/or regurgitation is a common and challenging condition in children and adults with congenital heart defects – of the 8 in every 1,000 live births that have congenital heart disease, 20% will have an RVOT problem. Surgical RVOT revision can be performed with a very low mortality, but valve conduits that are inserted to connect the right ventricle to the pulmonary artery have a limited lifespan, often less than 10 years, and as a result, the majority of patients with such conduits undergo multiple open-heart operations. The development of new, less invasive percutaneous methods to insert a heart valve without the need for open-heart surgery, with its potential complications, long hospital stay and long time off work/school, has the potential to significantly alter the life-long treatment of these patients. Research at UCL has advanced percutaneous pulmonary valve implantation (PPVI) through meticulous patient follow-up, computer modelling to identify procedural complications, technical improvements to the implanted device and definition of outcomes of success.

The first PPVI was performed in 2000 in a pilot case (one child) in Paris, France. In 2002, Professor Bonhoeffer moved to UCL to assess if implantation of the device could reduce the need for open-heart surgery in a broader patient group, taking advantage of UCL collaborators and the patient population at Great Ormond Street Hospital (GOSH). The next 220 patients who were recruited to studies of this valve implant were patients at GOSH/UCL. The first series was published in 2006 **[1]** establishing the feasibility and safety of the procedure, and detailed the haemodynamic consequences **[2, 3]**. Importantly, we determined that mechanical failure of one part of the stent occurred in 25% of cases, but that it was possible to detect this, monitor it and intervene in time to prevent adverse consequences **[3]**. Subsequently we established the optimal valve design, device implantation technique and patient selection for this procedure and monitoring schedule **[4, 5]**. This device was commercialised by Medtronic (Melody™), with CE marking obtained in 2006. Our research was the basis for the protocols for implantation of the valve, and training of the first 30 centres to use this technique was undertaken at UCL between 2005 and 2008.

Melody™ is only suitable for implantation into 15% of patients with pulmonary valve disease, because in the majority of patients the main pulmonary artery is too dilated for the procedure and such patients therefore still require open-heart surgery. We have used integrated computer-modelling techniques that utilise patient-specific data to design a new device that is suitable for a greater proportion of patients **[6]**. This new device – Native Outflow Tract Transcatheter Pulmonary Valve (TPV) – is in the process of being commercialised with Medtronic, and is currently in early phase clinical testing (three patients implanted so far).

## 3. References to the research

[1] Khambadkone S, Coats L, Taylor AM, Boudjemline Y, Derrick G, Tsang V, Cooper J, Muthurangu V, Hegde SR, Razavi RS, Pellerin D, Deanfield JE, Bonhoeffer P. Percutaneous pulmonary valve implantation in humans – Results in 59 consecutive patients. Circulation. 2005 Aug;112(8):1189-1197. http://dx.doi.org/10.1161/CIRCULATIONAHA.104.523266

[2] Coats L, Khambadkone S, Derrick G, Sridharan S, Schievano S, Mist B, Jones R, Deanfield JE, Pellerin D, Bonhoeffer P, Taylor AM. Physiological and clinical consequences of relief of right ventricular outflow tract obstruction late after repair of congenital heart defects. Circulation. 2006 May 2;113(17):2037-2044. http://dx.doi.org/10.1161/CIRCULATIONAHA.105.591438

[3] Nordmeyer J, Khambadkone S, Coats L, Schievano S, Lurz P, Parenzan G, Taylor AM, Lock JE, Bonhoeffer P. Risk stratification, systematic classification and anticipatory management strategies for stent fracture after percutaneous pulmonary valve implantation. Circulation. 2007 Mar 20;115(11):1392-1397. http://dx.doi.org/10.1161/CIRCULATIONAHA.106.674259

[4] Lurz P, Coats L, Khambadkone K, Nordmeyer J, Boudjemline Y, Schievano S, Muthurangu V, Yen Lee T, Parenzan G, Derrick G, Cullen S, Walker F, Tsang V, Deanfield J, Taylor AM, Bonhoeffer P. Percutaneous pulmonary valve implantation: impact of evolving technology and learning curve on clinical outcome. Circulation. 2008 Apr 15;117(15):1964-72. http://dx.doi.org/10.1161/CIRCULATIONAHA.107.735779

[5] Lurz P, Nordmeyer J, Muthurangu V, Khambadkone S, Derrick G, Yates R, Sury M, Bonhoeffer P, Taylor AM. Comparison of bare metal stenting and PPVI for treatment of RVOT obstruction: Utilization of an X-ray/MR hybrid lab for acute physiological comparison. Circulation. 2009;119(23):2995-3001. http://dx.doi.org/10.1161/CIRCULATIONAHA.108.836312

[6] Schievano S, Taylor AM, Capelli C, Coats L, Walker F, Lurz P, Nordmeyer J, Wright S, Khambadkone S, Tsang V, Carminati M, Bonhoeffer P. First-in-man implantation of a novel percutaneous valve – A new approach to medical device development. EuroIntervention. 2010 Jan;5:745-750. http://dx.doi.org/10.4244/EIJV5I6A122

## 4. Details of the impact

The research described above has resulted in a paradigm shift in the treatment of valvular heart disease. The wealth of data and experience generated through research at UCL was used for regulatory approval of the Melody™ device in Europe and Canada in 2006. The safety and effectiveness of PPVI have since been demonstrated in several additional studies performed by other investigators, including an FDA-sponsored trial in the US **[a]**. Importantly, the FDA trials were designed using our PPVI protocols and our imaging and clinical pre- and post-PPVI assessments. In 2007, NICE interventional procedure guidance (IPG 237) approved the use of the PPVI, with subsequent update in 2013 (IPG 436) **[b]**. FDA approval was obtained in the USA in 2010 for both the device and procedure **[c]**. Our data and subsequent protocol for monitoring valve fracture were instrumental in FDA approval.

Following approval, we were responsible for training practitioners from the first 30 centres to implement the procedure. All sites planning to implant the Melody™ device had to visit UCL/GOSH prior to becoming and approved implantation site, and for many sites, members of the UCL/GOSH team visited the site at the time of their first implantation **[d]**.

As a result of our invention, optimisation of implantation and monitoring, and training of cardiologists, the device and procedure is now used routinely in cardiac centres worldwide to treat patients with either narrowed or leaky pulmonary valves **[e]**. By July 2013, over 5,000 valves had been implanted in 35 countries worldwide **[f]**. Patients have therefore avoided open-heart surgery

with its greater risk of mortality and morbidity, its longer stay in hospital and its prolonged recuperation time. In 2012, the Melody device was awarded the Prix Galien USA 2012 award for Best Medical Technology **[g].**

The Melody device has also had significant commercial and economic impacts. With each device costing £17,000, total sales to date have been around £85m. There are also wider economic benefits due to the avoidance of open-heart surgery. A recent cost evaluation conducted in the US found that PPVI holds a significant cost advantage over the surgical approach for both health services and patients, since it requires fewer hospital days, and incurs less patient wage loss **[h]**.

Moreover the introduction of cardiac valves that can be implanted without the need for open-heart surgery has transformed the landscape of the management of valvular heart disease throughout the world, and is a paradigm shift in this field of cardiovascular medicine. Our work on the PPVI device has been at the forefront of this new wave of treatments. Although developed for the relatively small population of congenital heart disease, PPVI has established the way forward for much more common valve diseases in adults (transcatheter aortic valve and mitral clip). We have also influenced the way devices are designed, how they are introduced into man ('first-in-man' implantations), how patients are investigated prior to implantation and how they are followed up**.** The PPVI programme has gone hand-in-hand with the development of transcatheter aortic valve implantation (TAVI). Indeed, without the success of the PPVI programme, TAVI may not have developed as quickly, because in its early stage of development, TAVI mortality rates were very high (>60%), and the whole TAVI programme underwent ethical review in France. Our successful PPVI programme at UCL, with very low complication rates, permitted the TAVI programme to continue **[i]**.

The new device we have developed with Medtronic (Native Outflow Tract Transcatheter Pulmonary Valve (TPV) – shared IP with UCL/ GOSH) is in the process of being commercialised by Medtronic, and is currently in early phase clinical testing, with three patients implanted so far **[j]**. This new device can be used for many of the patients with right ventricular outflow tract disease (~1 in every 1,000 live births **[f]**) who are not suitable for Melody™, replacing open-heart surgery in these patients.

**5. Sources to corroborate the impact**

[a] Results from FDA-sponsored clinical trial:

- Zahn EM, Hellenbrand WE, Lock JE, McElhinney DB. Implantation of the melody transcatheter pulmonary valve in patients with a dysfunctional right ventricular outflow tract conduit early results from the U.S. Clinical trial. J Am Coll Cardiol 2009; 54(18):1722-1729 http://dx.doi.org/10.1016/j.jacc.2009.06.034

- McElhinney DB, Hellenbrand WE, Zahn EM et al. Short- and medium-term outcomes after transcatheter pulmonary valve placement in the expanded multicenter US melody valve trial. Circulation 2010; 122(5):507-516 http://dx.doi.org/10.1161/CIRCULATIONAHA.109.921692

[b] IPG436 Percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction: guidance. http://guidance.nice.org.uk/IPG436/Guidance/pdf/English

[c] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm199258.htm

[d] Example of training at one centre: http://www.dhzb.de/patients_visitors/dhzb_news/detail/ansicht/pressedetail/258/

[e] http://www.medtronic.com/melody/melody-system.html

[f] Email from Medtronic reporting that over 5,000 valves had been implanted by July 2013. Copy available on request.
Article reporting valves implanted in 35 countries by end of 2012: McElhinney DB, Hennesen JT. The Melody® valve and Ensemble® delivery system for transcatheter pulmonary valve replacement. Ann N Y Acad Sci. 2013 Jul; 1291:77-85. http://dx.doi.org/10.1111/nyas.12194.

[g] http://www.galienfoundation.org/hall-of-fame/pgu.php

[h] Vergales JE, Wanchek T, Novicoff W, Kron IL, Lim DS. Cost-analysis of percutaneous pulmonary valve implantation compared to surgical pulmonary valve replacement. Catheter Cardiovasc Interv. 2013 Jul 15. doi: http://dx.doi.org/10.1002/ccd.25128.

[i] 'Innovation and Fragility.' Somerville lecture, Capetown 2013. Phillip Bonhoeffer explains the history of the two programmes (see minutes 26-30) https://vimeo.com/76872760

[j] http://clinicaltrials.gov/show/NCT01762124