Institution: University College London		
Unit of Assessment: 12 - Engineering		
Title of case study: Improvements to patient health through implantable cardiovascular devices		
Period when the underpinning research was undertaken: 2006 - 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Gaetano Burriesci	**Role(s) (e.g. job title):** Professor of Bioengineering	**Period(s) employed by submitting HEI:** 2006 - date
Period when the claimed impact occurred: 2014 - 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Research at UCL Mechanical Engineering have led to the adoption of novel technologies in cardiovascular healthcare. Patient health and quality of life have been improved by the development of two new prosthetic devices now adopted worldwide (including, Italy, France and the USA): a semi-rigid ring for mitral annuloplasty that offers patients an improved physiological function and a sutureless artificial heart valve suitable for implantation with minimally invasive surgery. The devices have improved patient outcomes and, in the case of the sutureless valve, reduced surgeons' operating times. They have also brought commercial benefits to LivaNova by creating approximately 11% of LivaNova net sales for 2014-2020. The valve has now been implanted in over 50,000 patients worldwide.

2. Underpinning research

Professor Gaetano Burriesci is Chair of Bioengineering at UCL Mechanical Engineering, where he has been working since 2006. His expertise lies particularly in the definition of transformative healthcare treatments. The application of his research on novel material technologies, smart structures and advanced engineering approaches to medical devices is helping to address chronic heart diseases and improve patients' quality of life.

Mitral regurgitation, which occurs when the heart's mitral valve does not close properly, is one of the most common heart diseases, affecting (in its symptomatic form) about 8,000,000 patients across Europe and the USA. Traditional repair approaches have corrected this either by using rigid or flexible annuloplasty rings. Rigid rings are designed to provide a firm support to the valve annulus against dilatation, but prevent its physiological 3D motion, which have been shown to reduce the stress in the valve leaflets. Flexible bands maintain the annulus perimeter and its natural dynamics, but cannot enforce an optimum shape during the closing phase. Burriesci' s research into smart materials and structures produced the first semi-rigid annuloplasty ring that combines both features. It mimics the physiological 3D motion of the real mitral annulus whilst effectively reshaping the annulus conformation to improve systolic leaflets coaptation, as in rigid devices. This enhances the repair durability by reducing the stress levels applied on the mitral annulus and leaflets.

Professor Burriesci developed a cell-structure design with varying cell dimensions by combining the mechanical response of shape memory pseudo-elastic alloys – characterised by levels of recoverable strains up to 20 times higher than standard metals, they allow the ring to conform to the patient specific annulus with no changes in its mechanical response – with those of cellular auxetic structures. The latter are characterised by a negative Poisson's ratio and expand transversally when stretched, so that they enhance the structure's response to kinking (**R1, R2**). On joining UCL in 2006, Burriesci continued working on the implant development with Sorin Group SpA (now LivaNova Plc), thus initiating a UCL-LivaNova collaboration. The optimisation

of the prosthesis design was achieved through nonlinear finite element analyses, simulating the full manufacturing cycle and realistic operating conditions of the ring, to achieve the required functional rigidity in different regions of the device at safe levels of stress. The functional performance and lifetime of the prosthesis were assessed *in vitro* on prototypes, with clinical trials starting in 2007 and confirming the safety and efficacy of the device. The core patent for this invention was granted in 2009 in the EU and in 2011 in the USA. The concept was transferred into a novel device that received a CE mark (required for distribution in Europe) in 2007, and FDA approval in 2014. It is now marketed in several European countries, in the United States and Japan with the commercial names *MEMO 3D*™ and *MEMO 4D*™ (distributed by LivaNova Plc).

Burriesci developed a minimally invasive sutureless heart valve replacement for treatment of patients with degenerative aortic stenosis, a condition resulting from a progressive, age-dependent accumulation of calcium that disrupts blood flow across the aortic valve. It is one of the most common vascular heart abnormalities, affecting more than 10% of adults aged over 75. The advanced age of this population increases the risks of standard open-heart surgery, as it is commonly associated with co-morbidity and a past surgical history. In response to the needs of this rapidly growing patient population, Burriesci developed a sutureless self-anchoring cardiac valve prosthesis suitable for minimally invasive implantation. In contrast with standard surgical valves, the device comprises a frame made of pseudo-elastic alloy, supporting three leaflets of bovine pericardium. The frame is specifically designed to enable the delivery of the compressed valve through a transluminal delivery system, making its implantation less invasive than open surgery. The valve then self-expands into the anatomical region, where it self-anchors without requiring sutures (**R3**).

Burriesci continued to oversee the design of the device at Sorin. The crimping device used to load the valve into the delivery system (which is based on an array of wires rather than the more common wedge-iris mechanism, providing a more continuous and better-distributed radial force) (**R4**) was designed by Burriesci and previous colleagues since joining UCL. The patent describing the invention of the heart valve replacement was granted in 2010. The concept has been translated by Sorin Group (now LivaNova) into the sutureless surgical aortic valve Perceval™, which received the CE mark in 2011, FDA approval for the U.S. market in 2016 and regulatory approval for Japanese market in 2018. The patent for the invention relative to the crimping device used to load the Perceval™ into the delivery system was granted in 2010 in Europe and 2011 in the USA. Professor Burriesci and his team are now working on the development of an innovative aortic valve suitable for transcatheter implantation for a heart valve prosthesis with a deformable framework (**R5**) and a novel delivery system with a movable tether (**R6**). The device is currently at the *in vivo* preclinical evaluation stage.

3. References to the research

R1. Karnessis, N., **Burriesci, G.** (2013) Uniaxial and buckling mechanical response of auxetic cellular tubes. *Smart Materials and Structures* 22(8):084008. doi:10.1088/0964-1726/22/8/084008

R2. **Burriesci, G.**, and Bergamasco, G. (2011) "*Annuloplasty prosthesis with an auxetic structure*". European Patent n. EP 1 803 420 B1, available from https://worldwide.espacenet.com/publicationDetails/originalDocument?FT=D&date=20070704&DB=&locale=en_EP&CC=EP&NR=1803420A1&KC=A1&ND=4.

R3. Bergamasco, G., **Burriesci, G.**, Righini, G. and Stacchino, C. (2008) "*Cardiac-valve prosthesis*". World Intellectual Property Organization Patent n. WO2006085225 (A1). Available from https://worldwide.espacenet.com/publicationDetails/originalDocument?FT=D&date=20060817&DB=&locale=en_EP&CC=WO&NR=2006085225A1&KC=A1&ND=4.

R4. Righini, G., Bergamasco, G., **Burriesci, G.** (2011) "*Expandable prosthetic valve crimping device*". United States Patent application n. US 8006535 B2. Available from

http://worldwide.espacenet.com/publicationDetails/originalDocument?FT=D&date=20110830&DB=worldwide.espacenet.com&locale=en_EP&CC=US&NR=8006535B2&KC=B2&ND=4.

R5. **Burriesci, G.**, Zervides, C. and Seifalian, A. M. (2017) "*Heart valve prosthesis*". World Intellectual Property Organization Patent n. WO 2010 112 844 A1, Available from http://worldwide.espacenet.com/publicationDetails/originalDocument?FT=D&date=20101007&DB=worldwide.espacenet.com&locale=en_EP&CC=WO&NR=2010112844A1&KC=A1&ND=4.

R6. **Burriesci, G.**, Tzamtzis, S., Seifalian, A. (2012) "*Prosthesis delivery system*". World Intellectual Property Organization Patent n. WO2012052718 (A1), Available from https://worldwide.espacenet.com/publicationDetails/originalDocument?FT=D&date=20120426&DB=&locale=en_EP&CC=WO&NR=2012052718A1&KC=A1&ND=4.

4. Details of the impact

Both the semi-rigid annuloplasty ring and the sutureless heart valve invented by Professor Burriesci and described above have been on the market through Soringroup (now LivaNova) since 2007 (annuloplasty ring) and 2011 (sutureless heart-valve). Net sales of both products generated an average yearly revenue of approximately **USD115,000,000** (12-2019) between 2016 and 2019 in the US, Europe (such as UK and Italy) and the rest of the world. Both devices, marketed by LivaNova, are used globally in areas including Europe (such as UK, Italy and France), the US and Japan, and have collectively been used in over 300 cardiac centres in 34 countries across the world (**S1**). The sutureless valve, developed by Professor Burriesci is responsible for annual growth in Livanova sales and occurred despite a significant slowing of the overall market (**S2**).

Heart valves for surgical use constituted 11% of net sales for LivaNova between 2014 and 2020. For example, the LivaNova 2017 Year in Review specifies: "***Our Cardiac Surgery business also achieved record sales in 2017, driven by a number of products. […], and our Perceval® sutureless valve achieved 10 years of clinical use, with sales of Perceval growing double-digits every quarter in 2017***" (p3, **S2**). Similarly, their 2018 Annual Report indicates that, despite the worldwide decline in their heart valve sales, the device developed by Professor Burriesci increased its sales: "*Additionally, increased sales of our Perceval sutureless aortic heart valves were more than offset by a non-recurring sales return reserve of USD3,400,000 recorded during 2018 and continuing global declines in traditional tissue heart valve and mechanical heart valve sales.*" (**S2**).

Changed practice for cardiac surgeons

Professor Burriesci's research has improved patient health and benefited heart surgeons. Early clinical results have demonstrated the safety and efficacy of the **semi-rigid annuloplasty ring** to correct mitral valve regurgitation and confirmed the validity of the technical solutions adopted in the design. Efficiency of the novel design, the preoperative and postoperative mitral annular structures were compared and dynamics performance of different annuloplasty rings, concluding that "*Physio II and RSR could restore the physiologic three-dimensional annular shape, but the annular motion was diminished. Conversely, MEMO could preserve both the anteroposterior movement and folding dynamics, …"* (**S3**). This was also observed by assessing effects of different types of prosthetic rings on mitral annular dynamics, concluding that "*the annulus motion and annulus shape differed according to the type of prosthetic ring that was used*', and that '*Only the Memo 3D and Physio II rings allowed for the remodelling of the annulus, showing both a saddle shape and a normal AP/CC ratio during the systolic phase*" (**S4**).

A more recent clinical trial carried out on 17 patients using Professor Burriesci's technology confirmed that "*the Memo 3D ring demonstrates a saddle-shape configuration throughout the cardiac cycle despite its planar shape before implantation, which showed its shape to the physiologic dynamism of the mitral annulus*" (**S5**). Likewise, the sutureless valve has **facilitated minimally invasive procedures,** allowing at the same time **60% reduction in the procedure**

time (from 78 to 30 minutes of mean cross-clamp time), thus improving feasibility of combined procedures and related post-operative outcome (**S6**).

Improved health and welfare outcomes

The sutureless valve, which has now been implanted in **over 50,000** patients worldwide (**S7**), has likewise yielded substantial health benefits and **subsequent improvements to the quality of patients'** lives post-operation and returning to *'normality'* (**S8**) of their daily routine. For example, a former patient states: "*I had been suffering from aortic steno insufficiency for the last 7/8 years… I underwent the operation on May 30th so, 5 and a half months ago. To date I'm satisfied"* (**S8**). Similarly, another patient said: "*After no more than 20 days since I had left the hospital, I quickly returned to my normal life. Being small, the wound healed very quickly. After a week, I had no pain. I could do everything by myself".* In addition to patient benefit, the sutureless valve is improving clinical practice and reducing costs. A panel of 28 international experts with expertise in both minimally invasive aortic valve replacement and rapid deployment valves published a study that reports: "*The use of sutureless and rapid deployment valves reduces extracorporeal circulation and aortic cross-clamp time and leads to less early complications as prolonged ventilation, blood transfusion, atrial fibrillation, pleural effusions, paravalvular leakages and aortic regurgitation, and renal replacement therapy, respectively. These clinical outcomes result in reduced intensive care unit and hospital stay and reduced costs*" by approximately 25%. (**S9**).

In a Press Release from Livanova, dated 4 May 2017 (**S1**), both the devices invented by Professor Burriesci are highlighted and declarations from several end users are reported. Rakesh Suri, M.D., D.Phil., Cleveland Clinic and Cleveland Clinic Abu Dhabi said: "*From this prospective trial, the demonstrated hemodynamics and enhancements in patient quality of life support the practice and use of sutureless valves in patients with severe aortic valve stenosis.*" David Heimansohn, M.D., St. Vincent Heart Center, Indiana, said "***Since I began using the valve over 3 years ago, I have found that the use of Perceval is associated with a shorter procedure and recovery time, which allows patients to return back to their day to-day life more quickly***." These positive statements are reinforced by a clinician at the University of Brescia Medical School, Italy, who said "*With Perceval's technology, cardiac surgeons have a viable solution to standard bioprostheses that can decrease procedure time and reduce post-operative complications. These encouraging results demonstrated that the Perceval valve, when compared to TAVR (*transcatheter aortic valve replacement*), significantly improved patient outcomes for intermediate-risk patients with isolated aortic stenosis*".

In a recent analysis of the decennial experience with the Perceval valve published by Chuvette et al. (**S10**) the sutureless valve is highlighted: "*the rapidity of its deployment and its use in narrow spaces"*, the fact that "*it alleviates the excess operative risk associated with an annulus enlargement procedure"* and that the device is "*especially useful in minimally invasive procedures*" and in "*double or triple valve surgery, where the use of sutureless technology allows for significant reductions in CPB and cross-clamp times, favourable clinical outcomes, and excellent hemodynamic parameters*."

More recently, in a presentation given in 2019 at the American Association for Thoracic Surgery Meeting, Professor Bart Meuris from Leuven University Hospital (BE) presented data from the longest clinical follow-up for the Perceval valve (12-year clinical experience) (**S7**). The results regarding early stroke and mortality "*are better than those reported in both the surgical as the transcatheter arms of large trials comparing TAVR and SAVR in comparable patient cohorts*". The Perceval sutureless valve also "***offers a stable, time-saving and safe surgical result***, *both in isolated as in combined procedures. We observe promising long-term durability given the current low incidence of SVD* [such as structural valve deterioration] *after 11 years of continued clinical use*".

The technologies developed by Professor Burriesci are among preferred surgical treatment options used by leading clinicians. Patients also understand the benefits of the devices. For example, a retired music teacher who underwent valve replacement surgery, was inspired to

compose a song following her procedure where she says '*I am a proud possessor of a Perceval valve, you know that's sutureless, very important it's sutureless. And a five years study don't you see. So, I better keep going for 5 more years'* (**S8**).

5. Sources to corroborate the impact

S1. Press release articles (Businesswire; LivaNova)
S2. LivaNova earning press release and annual Reports (2014-2020)
S3. Ryomoto, M., Mitsuno, M., Yamamura, M. et al (2014) Is Physiologic Annular Dynamics Preserved After Mitral Valve Repair With Rigid or Semirigid Ring? *Ann Thorac Surg*. 97:492-498. doi: 10.1016/j.athoracsur.2013.09.077
S4. Nishi, H., Toda, K., Miyagawa, S. et al. (2016) Annular dynamics after mitral valve repair with different prosthetic rings: A real-time three-dimensional transesophageal echocardiography study. *Surg Today* 46: 1083. doi: 10.1007/s00595-015-1279-z
S5. Nishi, H., Toda, K., Miyagawa, S. et al. (2018) Annular dynamics of memo3D annuloplasty ring evaluated by 3D transesophageal echocardiography *Gen Thorac Cardiovasc Surg* 66: 214. doi: 10.1007/s11748-018-0886-1
S6. LivaNova: Product detail
S7. Szecel, D. and Meuris, B. (2020). Long-term outcome with sutureless valves: 12 years of Perceval experience. *Annals of Cardiothorac Surg* doi: 10.21037/acs.2020.04.03
S8. Youtube channel: patients testimonials
https://www.youtube.com/channel/UCcf7kxRsqwJGXJt8nm_c7VQ
https://www.youtube.com/watch?v=f2DK93OOtUA
S9. Glauber, M., Moten, S.C., Quaini, E. et al. (2016) International Expert Consensus on Sutureless and rapid deployment valves in aortic valve replacement using minimally invasive approaches. *Innovations (Phila)* 11(3): 165–173 doi: 10.1097/IMI.0000000000000287
S10. Chauvette,V., Mazine, A., Bouchard, D. (2018) Ten-year experience with the Perceval S sutureless prosthesis: lessons learned and future perspectives. *J Vis Surg*. 4:87. doi: 10.21037/jovs.2018.03.10