

Institution: University of Sheffield		
Unit of Assessment: A-03 Allied Health Professions, Dentistry, Nursing and Pharmacy		
Title of case study: The health and commercial impacts of research informing the development of the Cordella™ Heart Failure System		
Period when the underpinning research was undertaken: 2012-2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Dr Alex Rothman	Wellcome Trust Clinical Research Career Development Fellow	2012-present
Dr Andrew Swift	Wellcome Trust Clinical Research Career Development Fellow	2013-present
Period when the claimed impact occurred: 2014-2020		
Is this case study continued from a case study submitted in 2014? N		
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>Heart failure affects 26 million people worldwide, resulting in significant morbidity/mortality and health economic costs. Based on Sheffield research, Endotronix developed and brought to market the innovative Cordella™ Heart Failure System. This system permits daily, remote monitoring of pulmonary artery pressure and disease status to inform clinical decision-making and reduce hospitalisation, underpinning commercial and health impacts. Over 50 patients have been implanted with Cordella sensors in clinical trials, and over 200 patients use the Cordella™ Heart Failure System daily. Since 2016, the research has improved human health and underpinned commerce, involving more than \$100 million in direct foreign investment and the creation of 70 FTE jobs.</p>		
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>Background</p> <p>Heart failure affects 26 million people worldwide and accounts for 1 million inpatient bed days per year (2% of the NHS total) and 5% of emergency medical admissions, costing ~£2 billion (2% of the total NHS budget). Optimisation of medical therapy requires careful alterations in medications based on patient symptoms and key physiological parameters that are typically measured in a hospital setting. With commercial collaborators, Rothman and Swift conducted research to design and develop a novel heart failure management system that enables remote continuous monitoring of key physiological parameters; a central part of the research was the design of a sensor implanted in the pulmonary artery that wirelessly transmits arterial pressure measurements to a reader device held on the patient's chest (Figure 1).</p> <p>Procedure and Device Development: Proof-of-concept</p> <p>Rothman developed acute [R1] and chronic [R2] models of increased pulmonary artery pressure and heart failure in large animals to demonstrate the safety and accuracy of the pressure monitor and to develop techniques to be used to implant the device in patients. [Text removed for publication] using these models, it was demonstrated, for the first time, the safe delivery of the pressure monitor to the desired implant location, device stability at the implant location, accurate measurement of pulmonary artery pressure over a range observed in patients, stability and accuracy of the readings over prolonged time periods, and safe interactions of the device</p>		

with tissue at the implantation site (at a histological level) [R3]. [Text removed for publication] the development of a technique that facilitated percutaneous catheterisation lab-based implantation that critically contributed to securing funding and conducting the first-in-human study (the SIRONA study [R4]).

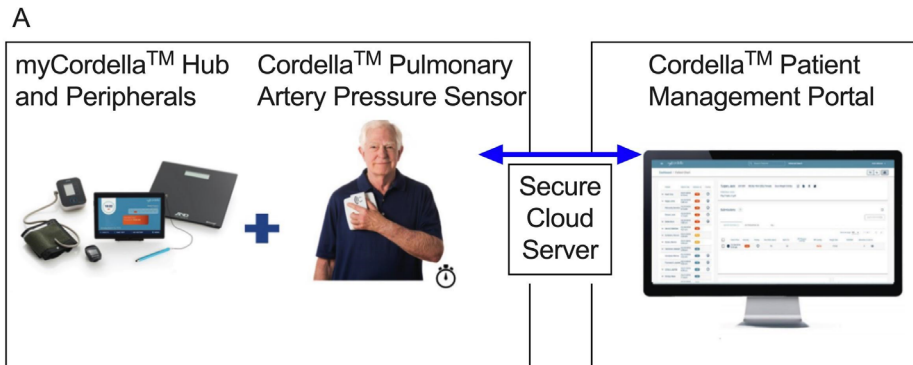
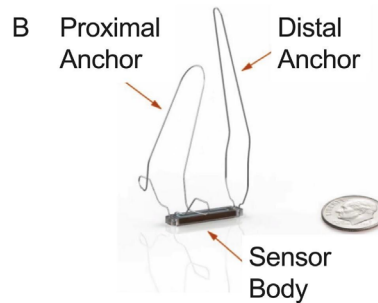


Figure 1: The Cordella™ Heart Failure System. (A) The Cordella™ System securely transmits daily health information (weight, blood pressure, saturations, heart rate) as well as pulmonary artery pressure data to clinicians from the patient's home. (B) The Cordella™ Pulmonary Artery Pressure Sensor.



Procedure and device development: Imaging the pulmonary arteries

The size and shape of the pulmonary artery in humans are not uniform. To ensure that a single pulmonary artery pressure sensor would be appropriately sized for the majority of patients, it was necessary to understand the relevant 3-D anatomy in a representative population. Based on research by Swift [R5], 3-D reconstructions of pulmonary arteries were made from a cohort of patients with heart failure from the UK (Sheffield) and the USA to evaluate the size distribution of the pulmonary arteries at the site of implant. Based on this work, the device anchors were sized in advance of the first-in-human study. For each patient enrolled the pulmonary arteries were reconstructed to identify the implant zone, optimise angiographic views and to measure vessel diameter and length and distance from the implant site to the location of the reader (Figure 2). This pre-procedure planning ensured device compatibility, readability and procedural safety.

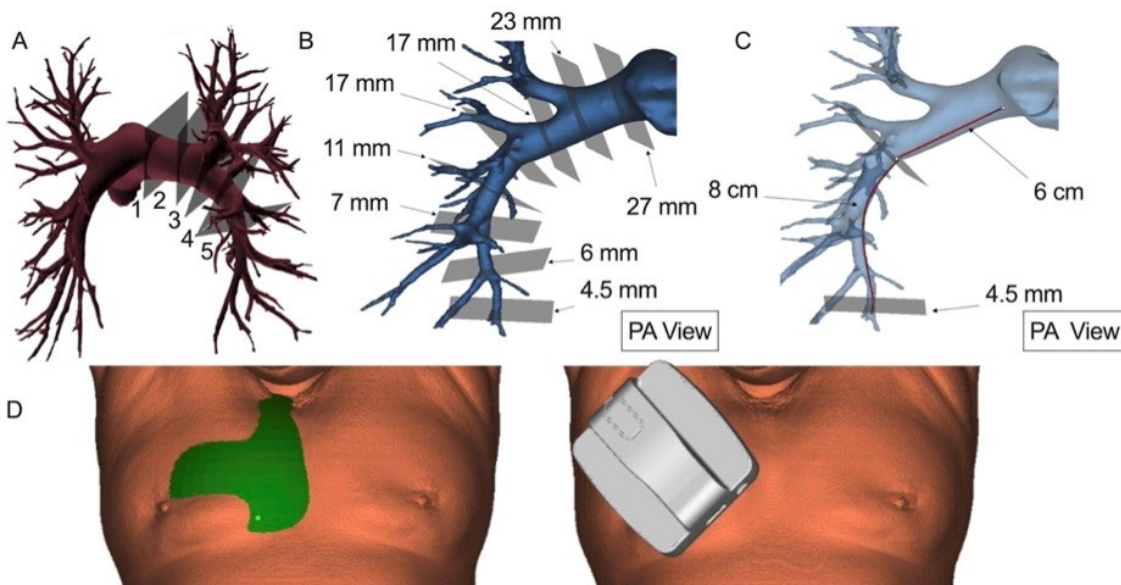


Figure 2: A - 3-D reconstruction of the pulmonary arteries of a patient with heart failure. Labels 1 to 5 represent angulated planes for measurement of size and curvature of the pressure monitor implant site. Multiple scans were analysed for determination of population mean and variance to size the pressure monitor. B-D – CT scans from individual patients enrolled in SIRONA were reconstructed to determine implant site dimensions (B), distal wire/catheter capacity (C) and reader area (D).

Procedure and device development: design iteration

Rothman led the first-in-human study undertaken at independent centres with staff without experience of interventional pulmonary procedures. [Text removed for publication]. In proctoring cases, Dr Rothman was scrubbed in the catheterisation lab when all implantations were undertaken, advising and training operators for independent implantation.

Two specific changes were made based on the anatomical [R5] and cath lab-based research [R3, R4]: 1- A change of nitinol anchors was made during the study to accommodate a broader range of patient and vessel sizes and to improve stability of the device. The imaging and 3-D reconstruction of the pulmonary arteries [R5] enabled iteration of the device, lengthening and angulating the distal anchor to stabilize the device on the inferior-posterior inflection of the pulmonary artery (Figure 3). 2- A device adjustment was initiated to make radio-opaque markers on the sensor asymmetric allowing the implanting physician to check orientation quickly (the device must face forward) and accurately during the procedure (Figure 3).

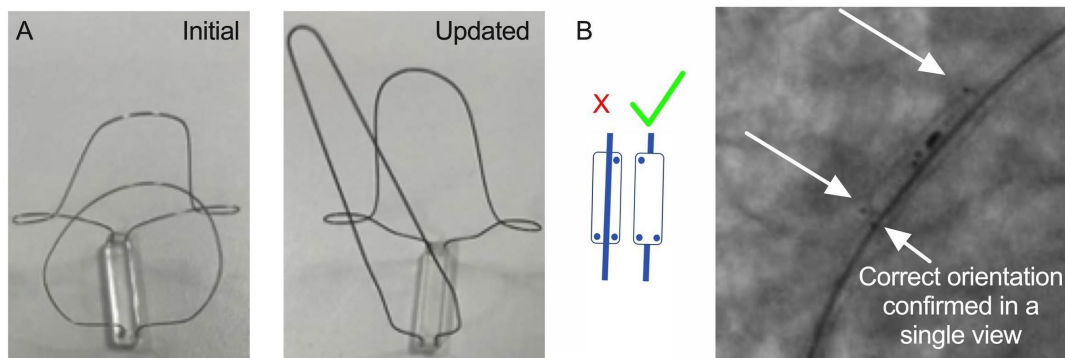


Figure 3: A - Initial and updated anchor configuration. B - asymmetric radio-opaque markers allow quick anterior-posterior alignment of device in a single x-ray view permitting rapid verification of correct orientation prior to implantation (white arrows point to radio-opaque markers).

3. References to the research (indicative maximum of six references)

- R1.** Rothman, A. M. K., Arnold, N. D., Chang, W., Watson, O., Swift, A. J., Condliffe, R., Elliot, C. A., Kiely, D. G., Suvana, S. K., Gunn, J., & Lawrie, A. (2015). Pulmonary Artery Denervation Reduces Pulmonary Artery Pressure and Induces Histological Changes in an Acute Porcine Model of Pulmonary Hypertension. *Circulation: Cardiovascular Interventions*, 8(11), e002569. <https://doi.org/10.1161/circinterventions.115.002569>
- R2.** Zhou, L., Zhang, J., Jiang, X.-M., Xie, D.-J., Wang, J.-S., Li, L., Li, B., Wang, Z.-M., Rothman, A. M. K., Lawrie, A., & Chen, S.-L. (2015). Pulmonary Artery Denervation Attenuates Pulmonary Arterial Remodeling in Dogs With Pulmonary Arterial Hypertension Induced by Dehydrogenized Monocrotaline. *JACC: Cardiovascular Interventions*, 8(15), 2013–2023. <https://doi.org/10.1016/j.jcin.2015.09.015>
- R3.** Rothman, A. M. K., Arnold, N. D., Abou-Hanna, J., Forouzan, O., Swift, A. J., Dahaghin, P., Konganige, S., Middleton, J. T., Zafar, H., Suvana, S. K., Kiely, D. G., & Gunn, J. (2020). Feasibility and safety of a telemetric pulmonary artery pressure monitoring system

in acute and chronic porcine models of pulmonary hypertension. *Preprint*.

<https://doi.org/10.1101/2020.12.27.424411>

- R4.** Mullens, W., Sharif, F., Dupont, M., **Rothman, A. M. K.**, & Wijns, W. (2020). Digital health care solution for proactive heart failure management with the Cordella Heart Failure System: results of the SIRONA first-in-human study. *European Journal of Heart Failure*, 22(10), 1912–1919. <https://doi.org/10.1002/ejhf.1870>
- R5.** **Swift, A. J.**, Dwivedi, K., Johns, C., Garg, P., Chin, M., Currie, B. J., **Rothman, A. M. K.**, Capener, D., Shahin, Y., Elliot, C. A., Charalampopolous, T., Sabroe, I., Rajaram, S., Hill, C., Wild, J. M., Condliffe, R., & Kiely, D. G. (2020). Diagnostic accuracy of CT pulmonary angiography in suspected pulmonary hypertension. *European Radiology*, 30(9), 4918–4929. <https://doi.org/10.1007/s00330-020-06846-1>

4. Details of the impact (indicative maximum 750 words)

University of Sheffield research led by Rothman and Swift, in part under a consulting contract with Endotronix [S1], provided crucial data and played an integral role in the development of the Cordella™ Heart Failure System, the sole product made by Endotronix [S2]. Endotronix brought this digital health platform product to the clinic, and became commercially available in Europe and the U.S. in 2020. The system assists clinicians in remote medical management of patients, allowing continuous monitoring of key physiological parameters and the observation of increases in pulmonary artery pressure up to 30 days prior to disease worsening and/or hospitalisation, contributing to reduced hospitalisation rates and health costs.

The Sheffield research contributed critical evidence that led directly to financing of \$32 million in July 2016 and \$12 million in Jan 2017 and that was used in a further funding round raising \$45 million in September 2018 [S2 and Figure 4].

Impact on commerce

The pre-clinical and clinical research carried out at Sheffield [R3, R4, R5] has been used to secure investment income of \$102 million since 2016 (foreign direct investment) and \$12 million in loans to develop the Endotronix Cordella Heart™ Failure System (the only product made by Endotronix) [S2]. Endotronix has made commercial sales in the USA, with Medicare and Medicaid reimbursement priced at [Text removed for publication]. As of July 2020, 50 patients had been implanted with the pulmonary artery pressure sensor with over 200 established on the online accessible care platform. The activities undertaken by Endotronix have led to the creation of **70 FTE** positions within the company in the current REF period [S2].

Impact on health

As of July 2020, 50 patients had been implanted with the Cordella Sensor in clinical trials, including a European-based CE-marked study and a US-based FDA investigational device exemption study. Rothman led implantation training for all sites, personally training and supervising (scrubbed in) at all sites [S2, S3]. [Text removed for publication].

As well as daily physiological monitoring with the ability to set individual patient goals, the Cordella™ Heart Failure System offers easy patient communication with the care team and provides guideline-directed education tools to engage and empower patients in the management of their disease. Based on patient feedback on Cordella, 87% of patients believe their health has improved since using the system, and 100% feel more connected to the clinical care team [S4]. Daily readings take <5 min, and 93% of patients say the system is easy to set up and easy to use on a daily basis [S4].

Based on his expertise in remote monitoring developed through the research [R4], Rothman led the development of a clinical service within the National Pulmonary Hypertension Service at the Royal Hallamshire Hospital in Sheffield. The service allows remote care to be provided for 60

patients, with pulmonary artery pressure monitors, insertable cardiac monitors, and remote monitoring systems, including the Cordella™ Heart Failure System [S4]. The service facilitates remote care for patients, reducing the requirement for repeated hospital visits and increasing the number of therapeutic changes made. For example, in data collected from the clinical service, the number of therapeutic changes made in the 12 months preceding device implantation was 10 increasing to 68 in the 12 months following implantation. Along with this, the number of disease-related hospitalisation events decreased from 21 before device implantation to 4 events in the post-implantation period [S5]. Daily remote data have permitted the optimisation of therapy without the need for repeated hospital visits, which has been of immense importance during the altered working practices due to the COVID-19 pandemic. High-risk patients with complex disease have been implanted with devices, with initiation of treatment prior to early discharge coupled with remote data-driven therapeutic escalation from their own homes. This approach has reduced time in hospital and improved the patient experience, increasing patient-expert physician contact and providing evidence-driven therapy in a manner not previously possible [S5].

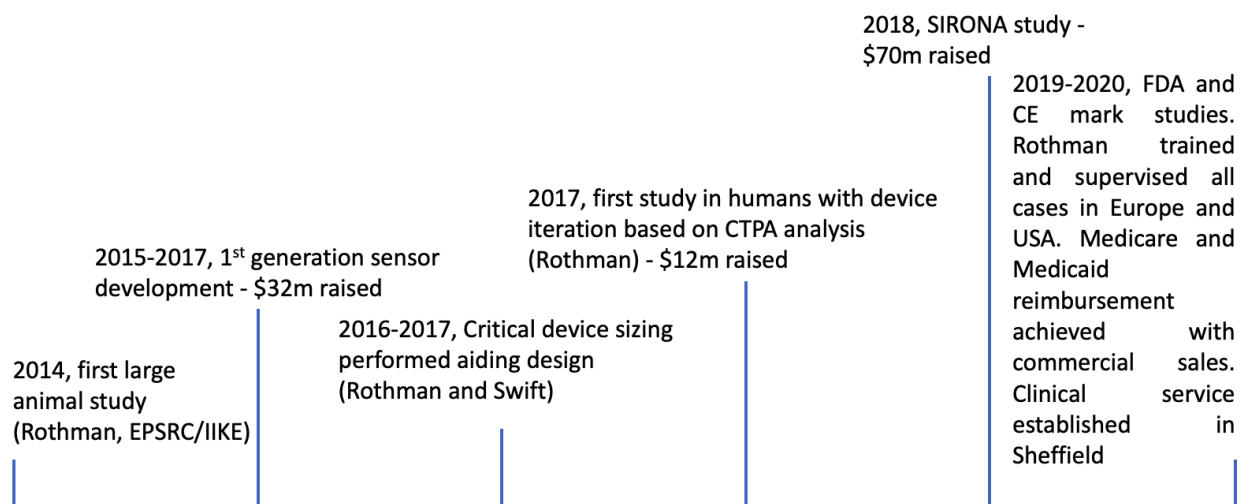


Figure 4: Summary timeline of Endotronix product development [S6]

5. Sources to corroborate the impact (indicative maximum of 10 references)

- S1. The University of Sheffield consulting contract number 5412.
- S2. Letter of support from the Endotronix CEO and founder confirming investment income, provision of crucial underpinning research (historic and ongoing scientific advisory board position) and number of jobs created.
- S3. Endotronix training and case review implant documents.
- S4. Endotronix usage, usability, and care data (<https://endotronix.com/heart-failure-management/>).
- S5. Letter of support from the head of the Sheffield Pulmonary Vascular Disease Unit.
- S6. Scrollable timeline of Endotronix product development (<https://endotronix.com/about-endotronix/>).