Institution: Coventry University		
Unit of Assessment: UoA3		
Title of case study: Safer Heart Therapies: Improving Drug Development and Patient Outcomes with InoCardia Ltd		
Period when the underpinning research was undertaken: August 2007-Dec 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:**
Prof. Helen Maddock:	Professor	2001-Present
Prof. Rob James	Professor	2011-Present
Dr Mayel Gharanei	Assistant Professor	2014-2020
Period when the claimed impact occurred: Aug 2013-Dec 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

Each year over $15bn of pharmaceuticals are sold which unintentionally cause or exacerbate heart disease. Since 2002 Coventry University researchers have developed a novel predictive Work-Loop assay, and complementary computational methods, to improve the early detection of adverse drug issues on heart contraction.

One result of this research was the successful spin-out company InoCardia Ltd., founded in 2013 to provide innovative services in cardiovascular safety assessment, creating revenue and jobs from its Coventry headquarters. Research has driven health sector innovation and productivity gains for [text removed for publication] and benefitted patient outcomes.

2. Underpinning research (indicative maximum 500 words)

One of the major reasons for safety-related attrition (drug failure) is adverse effects drugs can have on the cardiovascular system, including effects on the force of contraction of the heart (inotropy). Current cardiovascular tests used within the pharmaceutical industry cannot reliably predict drug effects on human hearts, and this often results in postponements or withdrawal to the development of safe and effective products.

Responding to this, CU's Professor Helen Maddock and Professor Rob James investigated the use of an in-vitro test, using heart tissue in the lab to closely mimic the physiology of the contraction and relaxation of the heart. This aimed to improve the safety assessment of drugs in development within the pharmaceutical industry, and reduce drug-induced cardiotoxicity [R1-3] [G1-8].

From 2000, initial research by Maddock using a functional working heart model [R4] [G1], and by James using skeletal muscle [R5] [G2], led to collaborative work where they developed a heart tissue in-vitro test referred to as the work-loop assay. This was capable of more closely simulating cardiac contractile physiology, mimicking the forces that are required to occur when the heart fills with blood in order for it to be pumped around the body, and enabled researchers

to successfully predict both the negative and positive side effects medical drugs would have on the heart, before the clinical testing stage [G3] [R1-3; R6].

Using papillary muscle, the work-loop assay was considered to be important to the pharmaceutical industry and in 2013 InoCardia Ltd. was founded to providing a cardiac drug safety assessment service for pharmaceutical companies, using an investment of £529,000 over four years from the Mercia Fund. From 2013-20 Maddock led on the development and expansion of their research portfolio and in collaboration with James, with InoCardia and CU respectively building InoCardia's cardiac safety assessment portfolio, supported by over £2.5m funding [G3-8] from InnovateUK, NC3R, European Development Research Fund and Horizon 2020.

From development of the initial academic research [R1; R3], InoCardia has optimised and industrialised the in vitro work-loop: the world's first non-clinical contractility assay which offers superior predictivity and is currently revolutionising the field of cardiac safety assessment [R1-3; R6]. The resultant 'Work-Loop Platform' is superior to competitor technologies in that it is better able to predict the risk that a new medicine may affect heart contractility in humans. The platform is validated for use by safety pharmacologists prior to experimental medicine entering clinic, to manage embedded inotropy risk.

Following funding from an EIT-Digital-Horizon 2020 award [G7] InoCardia launched an online virtual screen named 'The Contractome-AI'. Rather than physical testing in the lab, this provides users with the ability to perform risk-assessments on drugs using computer modelling, helping assess their safety far before they reach clinical trial stages [R6] [G7-8]. Research underpinning InoCardia's work received a recent 'Technological Innovation Award' from the global Safety Pharmacology Society in 2020, and in December 2020 Maddock was awarded a Women in Innovation award, recognising InoCardia's contribution to solving a pressing societal, environmental and economic challenges in the UK [G8].

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

R1. Mayel Gharanei, Afthab Hussain, Rob S. James, Omar Janneh, Helen Maddock (2014). Investigation into the cardiotoxic effects of doxorubicin on contractile function and the protection afforded by cyclosporin A using the work-loop assay. Toxicology in Vitro,Volume 28, Issue 5, 722-731. ISSN 0887-2333. https://doi.org/10.1016/j.tiv.2014.01.011.

R2. Rob Wallis, Mayel Gharanei, Helen Maddock (2015). Predictivity of in vitro non-clinical cardiac contractility assays for inotropic effects in humans — A literature search. Journal of Pharmacological and Toxicological Methods, (75) 62–69. ISSN 1056-8719. https://doi.org/10.1016/j.vascn.2015.05.009.

R3. Sophie Fletcher, Helen Maddock, Rob S. James, Rob Wallis, Mayel Gharanei, (2020). The cardiac work-loop technique: An in vitro model for identifying and profiling drug-induced changes in inotropy using rat papillary muscles. Scientific Reports 10, 5258. https://doi.org/10.1038/s41598-020-58935-2

R4. Rob. S. James, Robbie S. Wilson, and Graham N. Askew (2004). Effects of caffeine on mouse skeletal muscle power output during recovery from fatigue. Journal of AppliedPhysiology, 96(2):545-52. https://doi.org/10.1152/japplphysiol.00696.2003

R5. Maddock, H.L., Broadley, K.J., Bril, A. and Khandoudi, N. (2002), Effects of adenosine receptor agonists on guinea-pig isolated working hearts and the role of endothelium and NO.

Journal of Pharmacy and Pharmacology, 54: 859-867.
https://doi.org/10.1211/0022357021779041

R6. Mayel Gharanei, Adam Linekar, Oana Chuizbaian, Rob Wallis, Helen Maddock (2019). Physiological work-loop contractions using isolated myocytes. Journal of Pharmacological and Toxicological Methods, 99:106595. ISSN 1056-8719.
https://doi.org/10.1016/j.vascn.2019.05.059.

G1. James R. (PI) (2004). Effects of caffeine on mouse skeletal muscle power output during recovery from fatigue. Royal Society. Total grant: £50,000.

G2. Maddock H. (PI) (2007-2011). Development and optimisation of a cardiac work loop muscle model in normal and ischaemia / reperfusion conditions. Heart Research UK. Total grant: £85,000.

G3. Maddock H. (PI) (2012). Work-Loop marketing assessment. Mercia Fund, Pathfinder. Total grant: £30,000

G4. Maddock H. & James R. (PIs) (2014). Work-Loop Proof of Concept; KEEN96/A grant. Total grant: £58,225.

G5. Maddock H. & James R. (PIs) (2014-2016). InoCardia: Human Traberculae Work-Loop Feasibility. TSB/NC3R. Total grant: £249,500.

G6. Maddock H. & James R. (PIs) (2016-2020). InoCardia: Novel human-cell based assay for assessment of cardiovascular liability. InnovateUK/NC3Rs, Non animal technology award. Total grant: £982,075.

G7. Maddock H. (PI) (2019-20). Contractome-AI. EIT Digital, Horizon. Total grant: £873,617.

G8. Maddock H (PI) (2020). Delivering Improved Cardiac Safety Liabilities for Therapeutic Drugs Using the Contractome-AI. InnovateUK, Women in Innovation award. Total grant: £50,000.

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

As a consequence of CU's research, the commercially successful spin-out company InoCardia Ltd. has changed the face of drug development by offering new capabilities and knowledge within safety testing in pharmaceutical production, to improve patient health outcomes.

Spin-Out - InoCardia

In December 2013, InoCardia Ltd. was spun out from CU as a company specialising in the provision of predictive cardiac contractility assessment for early drug discovery. InoCardia is a successful self-funding business and has leveraged [text removed for publication] investor and public UK/EU funding from bodies including InnovateUK, NC3Rs, and EIT Digital [S1, G5-8], to develop the innovative Work-Loop Platform [S1]. Since its foundation the company has created seven full-time staff positions at its Coventry Headquarters and employs an additional three PhD students. InoCardia has worked with global pharmaceutical companies [text removed for publication] [S1] to screen new drugs in development, develop bespoke testing assays, and identify cardiovascular toxicity in exemplars from compound libraries [S1]. The novel assay has been used in the assessment of [text removed for publication], providing a predictive test approach to preclinical safety and efficacy assessment [S1].

Informing Drugs' Development

Both the *in-vitro* work-loop heart cell test and the Contractome-AI have established InoCardia as a world leader in cardiac contractility safety assessment, through better prediction of drug activity prior to clinical trials. InoCardia brings an 'entirely new approach to characterise drug effects on the full contractile/relaxation cycle in vitro' [S2; S3]. As the Senior Director of UCB Biopharma states, the Work-Loop Platform has 'greater predictivity to humans than existing tests' [S4; S5]. Safety Pharmacology Society (SPS) acknowledges InoCardia has enabled companies 'to better characterise drug treatment effects', taking into account 'the full contraction/relaxation phase of the contractile response' [S6]. The former Pfizer head of Global Safety Pharmacology attests that the assays 'add fundamental scientific knowledge and relevant improvements' in the relatively unexplored 'area of cardiovascular safety pharmacology' [S2].

Improving Drugs Testing and Production

InoCardia's radical approach is a major step forward in the production of safe, effective medicines. The effectiveness of the Work-Loop Platform has changed 'confidence in the predictivity of the *in vitro* assays' rather than *in vivo* animal testing, allowing project teams to make 'a better allocation of resources to compounds that have a greater chance of success' [S2]. The Work-Loop assay 'only requires milligram quantities of material' and therefore, 'can be used much earlier in the drug discovery process' [S2]. Therefore, pharmaceutical companies have reduced money they would have spent on the development of drugs doomed to fail at clinical trial; the 'ability to detect cardiac contractility issues earlier allows money (many millions of pounds) to be spent on compounds with a higher chance of success' [S4].

The most recent innovation from InoCardia, the *in-silico* Contractome-AI, has given pharmaceutical companies a pioneering new capacity to model compounds for cardiac contractility virtually, based on known qualities of components. Developed in collaboration with a computational chemistry-modelling company Cresset, used by eight of the top ten pharmaceutical companies, this has allowed an 'even earlier assessment of compounds' potential effects on cardiac contractility'[S7; S8]. As the Senior Director of UCB states, 'pharmaceutical companies of all sizes' can now make these savings, 'with no reduction in confidence in the compound safety' [S4]. Informed by InoCardia, the collaboration also drove 'scientific development of Cresset', which 'encouraged the company scientists to take a more holistic view of biological issues [S7; S8].

InoCardia's processes, underpinned by CU research, have driven gains in productivity, enhanced processes, and reduced waste. The company have also used their human tissue assay in safety assessments to advocate for technology that reduces and replaces animal use in research: in May 2017 Maddock organised a Safety Pharmacology Society meeting with NC3RS, which provided 'valuable information' on how use of 'human tissue in safety assessment has evolved', to inform and optimise practice [S6; S9, p.29]. InoCardia's innovative services have helped position the UK as a leader in new drugs development technologies which reduce animal tissue use, which according to the former Pfizer Head of Global Safety Pharmacology, marks a '…new era of drug discovery' [S2].

Improving Patient Health Outcomes

Further to improving patient health outcomes through improved drugs development, Maddock has also collaborated with University Hospital Coventry and Warwickshire (UHCW) to support improvements in the detection of cardiac injury in cancer patients. The research which underpins InoCardia's work has also given 'important clinical insight and knowledge in relation to therapy induced cardiac toxicity' in a clinical setting [S10]. It has 'provided fundamental scientific knowledge, research culture and support' to practitioners at UHCW, resulting in institutional change represented by the creation of a 'new and important collaborative multi-disciplinary Cardio-Oncology team between Oncology and Cardiology colleagues' [S10]. This has driven 'beneficial changes' in the clinicians' abilities 'to undertake research and improve clinical patient outcomes', as there was previously little formal collaboration between cancer treatment teams and cardiac health specialists, despite the negative responses the heart can have to radiotherapy [S10].

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

S1: Testimonial/report, CEO, InoCardia Ltd.

S2: Testimonial, Director, Vast Pharma Solutions, Former Pfizer Head of Global Safety Pharmacology.

S3: Testimonial, Senior Research Fellow, Translational and Quantitative Toxicology, Eli Lilly.

S4: Testimonial, Senior Director, Head of Investigative Toxicology & Safety Pharmacology, UCB BioPharma.

S5: Webpage. 'Artificial intelligence can deliver real benefits for patients', UCB BioPharma Website, 29.06.20. https://www.ucb.com/our-science/magazine/detail/article/Artificial-intelligence-can-deliver-real-benefits-for-patients [Accessed 02.03.21]

S6: Testimonial, Executive Director, Safety Pharmacology Society.

S7: Testimonial, Chairman and CEO, Cresset Group, Cambridge.

S8: Webpage. 'Cresset and InoCardia to develop 'in silico' cardiac safety assay for drug candidate screening', Cambridge Network Website, 09.06.20. <https://www.cambridgenetwork.co.uk/news/cresset-and-inocardia-develop-silico-cardiac-safety-assay-drug-candidate-screening> [Accessed 04.03.21]

S9: Jackson, S. J., Prior, H., Holmes, A. (2018) 'The use of human tissue in safety assessment', Journal of Pharmacological and Toxicological Methods 93, pp. 29-34, ISSN 1056-8719. https://doi.org/10.1016/j.vascn.2018.05.003.

S10: Testimonial, Clinical Oncology Consultant, Oncology and Radiotherapy Department, University Hospitals Coventry and Warwickshire.