Institution: University of Cambridge		
Unit of Assessment: 5		
Title of case study: Tackling cardiac rhythm abnormalities to extend and improve quality of life		
Period when the underpinning research was undertaken: 2000-2019		
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:**
Andrew Grace	Research Group Head and Consultant Cardiologist	1989-present
Period when the claimed impact occurred: 2014-2020		
Is this case study continued from a case study submitted in 2014? Y		

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

Problems with the rhythm of the heart (arrhythmias) are a major cause of sudden cardiac arrest, causing 4.5 million deaths annually worldwide. Research at the University of Cambridge from 2002 to 2019 aimed at understanding the fundamental biochemistry of electrical errors in the heart has led to the creation of the first subcutaneous implantable cardioverter defibrillator (S-ICD). Unlike other ICDs used to manage arrhythmias, the S-ICD does not need to be inserted into the heart's veins, greatly reducing risks of surgery and likelihood of failure. It particularly enhances quality of life for young patients facing a lifetime of device therapy or those at increased risk of infections. Since 2013, this device has been used to treat nearly 90,000 patients across 42 countries. The research has also led to a new diagnostic tool, AcQMap, commercialised in 2018, that allows for high quality imaging from inside the heart chamber, facilitating personalised treatment for the first time.

2. Underpinning research (indicative maximum 500 words)

Arrhythmias are heart rhythm problems, experienced by over two million people in the UK (NHS), including both ventricular (VF) and atrial (AF) fibrillation originating in the lower and upper heart chambers, respectively. VF is a common cause of Sudden Cardiac Arrest (SCA) with around 100,000 UK deaths annually making it the nation's biggest killer, more than lung cancer, breast cancer and AIDS combined (Arrhythmia Alliance, online). AF is responsible for 20% of strokes in the UK (Stroke Association, online).

Normal heartbeats are the result of electrical signals resulting from charge movements across cell membranes stimulating the heart chambers to contract. In 2002, Professor Andrew Grace of University of Cambridge and Royal Papworth Hospital, with academic/clinical collaborators, showed that disruption of the cardiac sodium channel leads to a severe ventricular defect. The decrease in total sodium conductance leads to slowed activation, providing a platform for understanding fibrillation [R1]. Prof. Grace predicted that slowed activation would predispose to fibrillation and could be inferred from electrocardiograms. In 2003, Prof. Grace and colleagues used paced electrogram fractionation analysis (PEFA) to show that slowed or delayed activation is a common feature in patients with non-coronary heart disease with a history of VF, and its assessment may allow the prospective prediction of VF risk in these patients [R2]. They went on to use PEFA as a predictor for SCA in patients with hypertrophic cardiomyopathy, the commonest cause for SCA in young people, and found that PEFA had a greater accuracy than alternative techniques at identifying patients at risk of SCA [R3].

A common method to manage symptoms and prevent the risk of SCA in patients is an ICD (implantable cardioverter defibrillator), a battery-powered electrical shock-generator that attaches directly to the heart for cardiac sensing and defibrillation, with leads inserted into the heart transvenously. However, these have high complication rates, including difficultly in

accessing veins and lead failure causing inappropriate shocks or impeding appropriate therapy. Prof. Grace and colleagues used their research as a platform to develop better devices, and created an entirely subcutaneous ICD (S-ICD), requiring neither direct contact with the heart muscle nor a transvenous lead. This was developed with the company Cameron Health, who used the underpinning research to file a patent in 2004 (US2004064177A1). They were subsequently acquired by medical device company Boston Scientific in 2012. Short-term clinical trials first identified suitable device configuration and energy requirements, which were then trialled to determine the subcutaneous defibrillation threshold compared to the transvenous ICD. The S-ICD consistently detected and converted VF induced during electrophysiological testing. All episodes of ventricular tachyarrhythmia were detected and treated [R4].

Prof. Grace and colleagues also improved diagnostic methodologies applicable to AF by developing an algorithm to accurately map cardiac activity; it processes multiple, simultaneous, noncontact voltage measurements within the cardiac chamber to derive the distribution of charge density (CD) sources across the surface of the heart chamber lining (endocardium). Myocardial charge sources are responsible for the electrical activity recorded in electrocardiograms, but traditional surface electrical recordings cannot resolve these sources. The cardiac activation mapping system comprises a multi-spine catheter with 48 ultrasound crystals each with unipolar electrodes. The catheter is inserted into the chamber of interest where the anatomy is defined by over 100,000 ultrasound points per minute on the endocardial surface. The key advantage of CD mapping is the ability to distinguish complex conduction patterns on the heart surface. Prof. Grace and colleagues' research into CD mapping found a four-fold improvement in resolution compared to voltage mapping, and a reduction in interference. This cardiac mapping technology was the first time that a source description of myocardial activity had been attained [R5]. As with the S-ICD, this has been developed with a commercial partner, Acutus Medical, to make the technology (AcQMap) available to improve outcomes for patients with atrial fibrillation.

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

R1. Papadatos GA, Wallerstein PMR, Head CEG, Ratcliff R, Brady PA, Benndorf K, Saumarez RC, Trezise AEO, Huang CL-H, Vandenberg JI, Colledge WH, **Grace AA**: Slowed conduction and ventricular tachycardia after targeted disruption of the cardiac sodium channel gene *Scn5a*. PNAS. 2002. 99(9) 6210-6215. DOI: 10.1073/pnas.082121299

R2. Saumarez RC, Chojnowska L, Derksen R, Pytkowski M, Sterlinski M, Sadoul N, Hauer RWN, Ruzyłło W, **Grace A**: Sudden death in non-coronary disease is associated with delayed paced ventricular activation. Circulation. 2003. 107:2595-2600. DOI: 10.1161/01.CIR.0000068342.96569.A1

R3. Saumarez RC, Pytkowski M, Chojnowska L, Sterlinski M, Sadoul N, Clague J, Connelly D, McLeod K, Morgan J, Cobbe SA, Griffith MJ, Bourke J, Huang C. L-H, **Grace AA**.: Paced ventricular electrogram fractionation predicts sudden death in hypertrophic cardiomyopathy. *European Heart Journal.* 2008. 29:1653-1661. DOI: 10.1093/eurheartj/ehn111

R4. Bardy GH, Smith WM, Hood MA, Crozier IG, Melton IC, Jordaens L, Theuns D, Park RE, Wright DJ, Connelly DT, Fynn SP, Murgatroyd FD, Sperzel J, Neuzner J, Spitzer SG, Ardashev AV, Oduro A, Boersma L, Maas AH, Van Gelder IC, Wilde AA, van Dessel PF, Knops RE, Lupo P, Cappato R, **Grace AA**: The Subcutaneous only Implantable Cardioverter Defibrillator New England Journal of Medicine. 2010. 363:36-44 DOI: 10.1056/NEJMoa0909545

R5. Grace A, Willems S, Meyer C, Verma A, Heck P, Dang L, Scharf G, Scharf C, Beatty G: High Resolution Non-Contact Charge Density Source Mapping of Endocardial Activation. *JCI Insight.* 2019. 4 (6): e126422. DOI: 10.1172/jci.insight.126422

All research outputs have been published in peer-review journals.

<u>Competitive funding received</u>

Medical Research Council - 2002-2007: Co-operative Group Grant on Translational Cardiovascular Biology. Atherosclerosis, Thrombosis and Arrhythmias, **GBP473,352**; 2002-2005: Calcium channels and cardiac arrhythmogenesis in the gene-targeted mouse, **GBP142,118**

Wellcome Trust - 2007-2010: Electrophysiological and molecular characterization of the cardiac conduction system in murine models of *SCN5A* sodium channel disease, **GBP372,044**; 2006-2009: A 500 MHz NMR spectrometer for high-throughput metabolomics to examine multifactorial diseases in mammalian systems, **GBP220,367***;* 2006-2009: Integrative Physiology of Cardiac Arrhythmias, **GBP573,072**; 2010-2013: Discovery and development of novel small molecule inhibitors of the human cardiac acetylcholine activated current for the treatment of atrial fibrillation, **GBP2,927,480**
British Heart Foundation - 2016-2020 – BHF Strategic Award – **GBP10,000,000**. 2008-2011: Genetic determinants of triggering/perpetuation of atrial fibrillation, **GBP228,000**; 2002-2005: Molecular physiology of cardiac sodium channel mice, **GBP128,609**, 1998-2001: Development and characterization of a gene targeted model of human LQT3, **GBP188,007**.
BBSRC - CASE studentship (2008-2011), Atrial Fibrillation Triggering **GBP94,000**.
NHS Executive Research and Development Programme*.* 2000-2003: A review of the evidence on the effects and costs of ICD therapy in different patient groups and modeling of cost-effectiveness and cost-utility for these groups in a UK context, **GBP54,461**.
European Heart Rhythm Association 2017 – Clinical Research Fellowship for Dr Jakub Baran, **EUR25,000**; 2019-2020,
Società Italiana di Cardiologia, Research Fellowship for Andrea Porto – **EUR25,000**

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

Research undertaken at the University of Cambridge into the biochemical underpinnings of cardiac arrhythmias has led to the development of a device and a diagnostic mapping approach, which have improved outcomes for affected patients, as well as contributing to the economy via the companies developing the technologies.

Subcutaneous implantable cardioverter defibrillator (S-ICD)

Commercial activity

Founded on Cambridge University research, the S-ICD is the first and only commercial subcutaneous implantable cardiac defibrillator, available from Boston Scientific. In a December 2020 letter to healthcare professionals using the S-ICD they describe use of the device in almost 90,000 patients [E1]; in their 2019 annual report, they disclosed Cardiac Rhythm Management sales of USD1,939,000 [E2]. It was named the most innovative product in electrophysiology at the EHRA Europace CARDIOSTIM global medical conference in 2014 [E3] and is available in 42 countries across the Americas, Asia, Australasia, Europe, and the Middle East (Boston Scientific, find an implanting centre, online).

Even though it is a relatively new technology currently only available from a single supplier the S-ICD has still established itself in UK healthcare, where in 2019 it accounted for 20% of single chamber implants (the usual type for primary prevention of sudden arrhythmic death, approx. 3500 total in 2018/19) [E4, page 12]. The National Audit of Cardiac Rhythm Management (NACRM) 2020 from the British Heart Rhythm Society states that use within suitable patients in the UK is likely to increase as competitors bring new functionality to the market and drive prices down [E4, page 11]. The S-ICD's lack of leads in the heart means it cannot act as a pacemaker so will not fully replace standard ICDs; however, it can address the risks of conventional ICDs for that proportion of patients whose need is solely for defibrillation shocks [E4, page 3].

Regulatory approval and recommendations for treatment

Globally, the S-ICD is recommended as a treatment option by: the US Food and Drug Administration (FDA, 2012), the European Society of Cardiology (ESC, 2015), and the UK National Institute for Health and Care Excellence (NICE, 2017) [E5, pages 8 and 35]. In their support, the ESC describe how the S-ICD is a good option for patients who show issues with access to the heart via the vascular system or recurring problems with transvenous leads, such as young patients facing a lifetime of device therapy or patients at particular risk of infection. They cite a trial of 330 patients where there were no lead failures or complications associated with lead placement, and all induced arrhythmias were successfully controlled [E5, page 35].

Director of Electrophysiology at the Deborah Heart and Lung Centre, New Jersey, USA said "In those patients that are young and otherwise not in need of pacing…the subcutaneous ICD is the way to go" [E6]. Director of Cardiac Electrophysiology and Arrhythmia Services at Cooper University Hospital, New Jersey, USA said, "With the S-ICD there's…a zero risk of having a transvenous infection from the device" [E6].

In clinical trial (NCT01296022) results from the University of Amsterdam of 849 patients across 39 centres in Europe and the USA (N Engl J Med 2020; 383:526-536), the positive outcomes resulted in a recommendation that the S-ICD should be considered in all patients in need of an ICD without pacing, not just as a niche option for particular cases. Results from another trial of 1111 patients across 110 sites, many with more complex conditions, showed "high S-ICD efficacy and safety despite the sickest cohort studied to date" [E7].

Quality of life for treated patients

As well as these clinical data on the efficacy of the S-ICD, there is impact in terms of improving quality of life for those who receive the device. One patient previously had a transvenous ICD for nine years, until she collapsed due to a fracture in one of her leads. After replacement with the S-ICD, she said she "finally felt safe" [E8]. One patient, who experienced SCA whilst wake-boarding with friends, said, "Now that I have the…device I'm back to like my old self. I can exercise, I can play sports again. I can go back to wake boarding and jump off 70ft cliffs and give my mum a heart attack and not have to worry about having one myself" [E8]. Another advantage of the S-ICD is that it is fitted underneath the arm where it is much less visible than transvenous ICDs which are fitted to the front of the chest. One patient has spoken of the impact of the S-ICD on her life. She said, "The first time I put on a sports bra to go for a run, I just started crying because you couldn't see it." [E8]. Such examples show the value of the S-ICD in helping patients live as normal a life as possible.

AcQMap

Product development

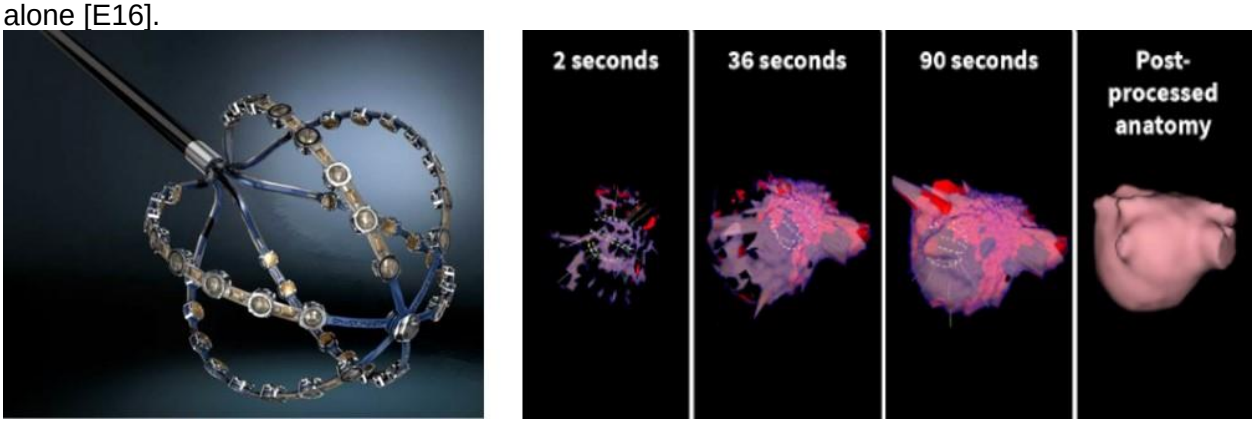
For patients suffering with atrial fibrillation (AF), ablation therapy (catheter ablation) is an option for patients who wish to avoid or cannot tolerate medication. Heat (radiofrequency ablation) or freezing (cryoablation) are used on the area of the heart causing the arrhythmia, creating scar tissue which breaks abnormal circuits in the heart and destroys areas of the heart muscle which are triggering arrhythmias (British Heart Foundation, online). The accuracy and effectiveness of the treatment is closely linked to how well the arrhythmia can be mapped in the heart prior to and during treatment, usually performed by electrocardiograms (ECGs). Prof. Grace's work to accurately map cardiac activity was used to develop AcQMap with the company Acutus Medical, brought to market in 2018. It is the first and only all-in-one 3D imaging and heart mapping system. A 25mm catheter inserted into the heart enables visualisation of complex arrhythmia, with the unique and personalised images of a patient's heart, guiding therapy to very specific targets within the heart chambers that are responsible for causing atrial fibrillation [E9].

Clinical trial successes

The number of catheter ablation procedures carried out for AF has risen, with over 6000 procedures being performed annually in the UK, (~100 per million population, BMJ 2019;367:l6428) There is a need for accuracy to improve patient outcomes and to avoid the need for repeat procedures. In a clinical trial of 129 patients from 2016 to 2017 (prior to commercialisation by Acutus), the use of the novel, noncontact imaging and mapping system to guide ablation therapy showed a safety outcome of 98% with no major adverse events reported. A marker of effectiveness of treatment is one year of freedom from AF following catheter ablation therapy; this is usually around 43% for a single procedure and 69% for more than one procedure. In this trial, after 12 months 72.5% of patients were free from AF following a single procedure, and 93.2% were AF free after a second procedure, indicating significant improvement in terms of targeting ablation where it is needed [E10].

Regulatory approvals and commercial investment

In 2016 AcQMap received the EU CE mark [E11, page 1] and FDA approval in 2017, then in 2020 for an updated version [E11, pages 3 and 15]. When Acutus launched the product in 2018, they secured investment of USD75,000,000 [E12]. In 2019, Acutus generated AcQMap sales of USD2,800,000, and in 2020 raised USD163,300,000 in its initial public offering on the US stock exchange [E13]. In their Third Quarter 2020 Results, published on 12 Nov 2020, Acutus stated that as of 30 Sep 2020 there were 49 AcQMap consoles installed worldwide (countries not disclosed), 21 of these within the last quarter [E14]. While it is difficult to contextualise market share for a novel, emerging technology, the level of investment secured, the approvals granted and uptake in clinics indicate confidence in AcQMap and the benefits of its use. AcQMap is currently available within the UK and EU as a part of a 100-patient clinical trial for which Prof. Grace is a principal investigator, showing his continued involvement in the development and use of the technology [E15]. It is being trialled at 15 locations within the UK, and as of July 2020, AcQMap had benefitted more than 80 patients at the Royal Papworth Hospital in Cambridge alone [E16].



L: The AcQMap (Acutus Medical), R: Ultrasound reconstruction of the left atrium using AcQMap. Post-processing is performed to establish the final anatomy [E9]

Patient quality of life improvement

The significance of AcQMap for health and wellbeing is highlighted in the case of one patient from the UK who said, “Life with atrial fibrillation was hard work and debilitating... I had a standard ablation for atrial fibrillation to try and treat the problem, but…it didn’t help improve my condition...the AcQMap trial…immediately had a positive impact. My heart went back into normal rhythm... I’ve got a new lease of life and enjoying every day to the full” [E9].

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

E1. Letter from Boston Scientific to healthcare professional using the S-ICD
E2. Boston Scientific Annual Report 2019, page 5 of publication (page 7 of PDF)
E3. BSC press release
E4. National Audit of Cardiac Rhythm Management 2020
E5. S-ICD approvals and guidelines from the US Food and Drug Administration, European Society of Cardiology and National Institute for Health and Care Excellence (key information, pages 8 and 35)
E6. Clinician testimonials: www.youtube.com/watch?v=one8JMcGZDY
E7. S-ICD clinical study article
E8. S-ICD patient testimonials: youtube.com/watch?v=YpBux7p014w; youtube.com/watch?v=5ES5_AKAN-M; youtube.com/watch?v=eaP4B3t-cmw
E9. News article: Atrial fibrillation: AcQMap device revolutionises treatment for patients
E10. Willems S, Verma A…Grace A. (2019). Circ Arrhythm Electrophysiol. 12(7):e007233.
E11. AcQMap approvals: CE mark from EU (2016), FDA (2017, 2020)
E12. Article detailing USD 75,000,000 investment secured by Acutus for AcQMap
E13. Article detailing Acutus IPO and sales data
E14. Acutus Medical third quarter 2020 results
E15. UNCOVER AF clinical trial details
E16. NHS press release