Institution: University of Hull

Unit of Assessment: A3: Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Improving well-being and outcome for patients with heart failure using Cardiac Resynchronisation Therapy (CRT)

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

Hull researchers conducted the key trial demonstrating that cardiac resynchronization therapy (CRT), a specialised type of pacemaker, significantly reduces morbidity and mortality and improves the quality of life of selected patients with heart failure. CRT has become a cornerstone of treatment for heart failure and a standard recommendation in clinical guidelines world-wide. Over a 5 year period about 40,000 people in the UK have had pacemakers implanted; about 8,000 of these patients would be projected to have died within 5 years if they had not received CRT. The world market for CRT devices is projected to grow to $2.8 billion annually by 2015.

2. Underpinning research (indicative maximum 500 words)

Heart failure is common and affects all ages and nations. Conservative estimates suggest that heart failure affects about 10,000 people per million population or about 70 million people worldwide, of which about 4 million will be in the European Union. Without modern treatment, approximately one third of patients will die within 6 months of the onset of heart failure and most others within 3-5 years.

In about half of patients, heart failure will be due to weakened contractions of the left ventricle (the main pumping chamber of the heart); this is called systolic dysfunction. In health, the heart has a highly organised, sequential and coordinated pattern of contraction. In patients with systolic dysfunction, this may be disrupted (this is termed cardiac dyssynchrony) and cause further deterioration in the heart's performance.

Researchers at Hull led a major, multi-centre, randomised controlled trial (CARE-HF) comparing a strategy of implanting CRT or not amongst patients with moderate or severe symptoms of heart failure over and above best standard medical therapy. Professor Cleland was the Chief Investigator and chaired the steering committee that designed, led and interpreted the outcome of the study. CARE-HF was conducted in 82 centres in 12 Western European countries, enrolling 813 patients between 2001-2003. Follow-up for the main study was completed in late 2004 and results reported early in 2005 in a highly cited paper in the New England Journal of Medicine (1). Follow-up continued until 2009 (2) with further results being published in 2012 (3). Altogether, analyses of the data generated by this study have led to >30 publications, including two in high-impact journals in 2013.

The primary outcome measure of CARE-HF was time to death or first unplanned hospitalisation for a major cardiovascular event, which was reached by 159 patients in the CRT group compared with 224 patients in the medical-therapy group (39 percent vs. 55 percent; hazard ratio, 0.63; 95 percent confidence interval, 0.51 to 0.77; P<0.001) over a median follow-up of 29 months. There were 82 deaths in the CRT group, compared with 120 in controls (20 percent vs. 30 percent; HR 0.64; 95%CI, 0.48 to 0.85; P<0.002). CRT also improved cardiac function, symptoms and quality of life scores (all P<0.01, Ref 1). A 6-month extension phase showed an even greater effect on mortality with 154 deaths (38.1%) in the control group and 101 (24.7%) in those assigned to CRT (HR 0.60, 95% CI 0.47–0.77, P=0.0001) due to a reduction both in sudden deaths and death due to heart failure (2).

Long-term follow-up until 2009 suggested that the benefits of CRT were maintained although the control group outcome had improved somewhat as most survivors received a CRT device after the results were reported (3). Life-time projected cost-effectiveness analyses indicate this is highly cost-effective with an estimated cost of about 7,000 euro per life-year gained, with or without

adjustment for quality of life (4).
The effectiveness has been confirmed in Professor Cleland's recently published individual patient-data meta-analysis of five landmark studies with almost 4,000 patients. It also showed that the duration of the QRS interval (the electrical signal leading to ventricular contraction) on the electrocardiogram is the only useful guide to response. Patients with a QRS of >140msec are more likely to benefit from treatment (6).

Researchers in Hull who contributed to the CARE-HF study:
Professor John Cleland (January 1999 to September 2013); Dr Gerry Kaye (patient identification, implantation and ECG adjudication January 1999 to October 2006), Dr Justin Ghosh (ran core data laboratories – March 2001 to October 2006).

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

1. Cleland, JGF., Daubert, J-C., Erdmann, E., Freemantle, N., Gras, D., Kappenberger, L., Tavazzi, L., for the Cardiac Resynchronization — Heart Failure (CARE-HF) Study Investigators. The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure. N Engl J Med (2005);352: 1539-49. (Cited 3,966 times up to August 2013).

2. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. Eur Heart J. 2006 ;27:1928-32. (cited 381 times up to August 2013).

3. Cleland JG, Freemantle N, Erdmann E, Gras D, Kappenberger L, Tavazzi L, Daubert JC. Long-term mortality with cardiac resynchronization therapy in the Cardiac Resynchronization-Heart Failure (CARE-HF) trial. Eur J Heart Fail. 2012; 14: 628-34. (cited 19 times up to August 2013).

4. Yao, G, Freemantle, N., Calvert, MJ., Bryan, S., Daubert, J-C., **Cleland, JGF**. The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. European Heart Journal (2007); 28: 42–51 (cited 123 times up to August 2013).

5. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: The Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, **Cleland J**, and others. Eur Heart J. 2013; 34: 2281-329.

6. Cleland JG, Abraham WT, Linde C, Gold MR, Young JB, Claude Daubert J, Sherfesee L, Wells GA, Tang AS. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. Eur Heart J. 2013 Jul 29. [Epub ahead of print]

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

Presentation of the results of CARE-HF in 2005 had an immediate effect on all subsequent clinical guidelines related to Heart Failure. The UK (NICE), European Society (that also covers Russia, Middle East and North Africa), North America, Australia and New Zealand and many other national guidelines around the world, including the latest guidelines in 2013 have endorsed the original recommendations based on CARE-HF, which stands out as the landmark study in this field. As a consequence of CARE-HF, Professor Cleland has been invited to inform many and develop some of these practice guidelines.
For example, the 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy state:- "*CARE-HF, with a 29-month follow-up period, was the first study to show a reduction in total mortality by CRT, compared with control, but without significant lowering of the risk of sudden cardiac death. However, in the extension study with a 37.4-month follow-up time, 46 there was a*

significant 5.6% reduction in the absolute risk of dying suddenly" (Reference 5. Eur Heart J. 2013; 34: 2281-329)

The ACC/AHA guidelines on heart failure state:- "*Pharmacological therapy is not a consistent determinant of HRQOL; therapies such as ACE inhibitors and angiotensin-receptor blockers (ARBs) improve HRQOL only modestly or delay the progressive worsening of HRQOL in HF. At present, the only therapies shown to improve HRQOL are cardiac resynchronization therapy (CRT) and certain disease management and educational approaches" and* "*These results have included a decrease of approximately 30% in rehospitalization and reductions in all-cause mortality in the range of 24% to 36%. Improvement in survival is evident as early as the first 3 months of therapy."* (Source 1).

The National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand stated that: *"Two key placebo-controlled RCTs [Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) and Cardiac Resynchronization in Heart Failure Study (CARE-HF)] ….showed that CRT reduced the risk of death from any cause and hospital admission for worsening HF ….[RRR in death of … 36% with CRT-P in CARE-HF]. In CARE-HF, the RRR in HF hospitalization with CRT-P was 52%. These benefits were additional to those gained with conventional treatment, including a diuretic, digoxin, an ACE inhibitor, a beta-blocker, and an MRA."* (Source 2).

The NICE guidelines, introduced in 2007, were further revised in 2010 (Source 3) and stated that: *"Cardiac resynchronisation therapy (CRT) is one of the major new advances in the management of heart failure, resulting in reduced morbidity and increased survival of heart failure patients with dys-synchrony. The Guideline Development Group were aware of new advances in the evidence-base for CRT, widening the indications for these devices to involve patients with less severe heart failure"*.

There is evidence that clinical guidelines have and continue to have an impact on clinical practice. There are about 10,000 people with heart failure per million people in the UK, of which about 400 per million per year (pmpy) may become suitable for CRT. Currently about 120 pmpy population are recorded as receiving these devices (under-reporting is considered likely) in the UK with rates doubling from 2007 to 2011 (Sources 4 and 5). On current estimates, over a 5 year period about 40,000 people in the UK will receive these devices and, of these, 8,000 more would expect to be alive at 5 years as a result. The increase in use has been even greater in other countries. In Italy and Germany (Source 5), implantation rates are substantially greater than in the UK. In the USA CRT implantation has risen from about 40,000 devices in 2006 to 110,000 in 2010 (>300 pmpy; Source 6).

Of 7 billion people worldwide, 2.8 million will become eligible each year for CRT. This means millions more patients with heart failure have increased survival beyond 5 years due to the seminal work in Hull on CRT. A third major beneficiary of the CRT study has been the companies who make these devices (Medtronic, Boston-Scientific, St Jude, Sorin, Biotronik). The anticipated growth in the world-market will certainly stimulate further innovation and improvement. The world market for CRT devices is estimated to grow to about $2.8 billion annually by 2015 (Source 7).

The Cardiomyopathy Association - a patient-led organization (source 8) and the British Heart Foundation (Source 9) both highlight the importance of CRT as a treatment option for patients suffering with left ventricular systolic dysfunction. These public information web-sites receive thousands of hits per year reflecting the significant reach of the research findings. The key beneficiaries of the work on CRT are patients. CRT reduces the annual risk of death by about 40%, with 21 more patients alive at 5 years for every 100 patients treated. This is a large effect compared with most other treatments in heart medicine (e.g. a much larger effect than heart bypass surgery). In addition to the effects on mortality, many patients also experience improvement in symptoms and quality of life. CRT reduces the risk of recurrent hospitalisations for worsening heart failure which may largely offset the cost of device implantation. Health economic analyses suggest that CRT is highly cost-effective (Reference 4 above) and so is an efficient use

of health service resources.

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

1) 2009 Focused Update (Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults). A Report of the American College of Cardiology Foundation/American Heart Association. Task Force on Practice Guidelines. Journal of the American College of Cardiology (2009) Vol. 53, No. 15.
http://content.onlinejacc.org/article.aspx?articleid=1139601
2) Guidelines for the prevention, detection and management of chronic heart failure in Australia (Updated July 2011). National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand.
http://www.heartfoundation.org.au/SiteCollectionDocuments/Chronic_Heart_Failure_Guidelines_2011.pdf
3) NICE Clinical Guideline No 108 CHRONIC HEART FAILURE
National clinical guideline for diagnosis and management in primary and secondary care
August 2010 http://guidance.nice.org.uk/CG108
4) NICOR CRT implant rates https://nicor4.nicor.org.uk/CRM/device.nsf/65153b7e3756850e80256aff003a2c78/$FILE/ CRM%20National%20Clinical%20Audit%20Report%202010.pdf Page 16
5) The EHRA White Book. Europace (2012) 14 (suppl 3): ii1-ii55 doi:10.1093/europace/eus256
6) http://www.hrsonline.org/Practice-Guidance/Quality-Outcomes-Reporting/ICD-Registry#axzz2YBdHfWr4
7) http://finance.yahoo.com/news/research-markets-global-cardiac-resynchronization-160700751.html (Release 01/07/2013)
8) Cardiomyopathy association, http://www.cardiomyopathy.org/index.php?id=1163
9) BHF http://www.bhf.org.uk/plugins/PublicationsSearchResults/DownloadFile.aspx?docid=085ff7a4-1073-44ab-b7b3f539579e091a&version=1&title=Pacemakers&resource=HIS15