Institution: University of Sussex

Unit of Assessment: UoA10

Title of case study: The statistical analysis of heart-surgery data influences practice guidelines and choice of procedures

1. Summary of the impact

The statistical analysis of large datasets has contributed to the rehabilitation of the Ross procedure (the replacement of a failing aortic valve with the patient's own pulmonary valve) for specific patient groups, such as those above 50 years old who want to avoid daily anticoagulation treatment, and those with a reduced life span, especially patients on dialysis. The results of the research have (a) contributed to changes in the current practice guidelines of the European Society of Cardiologists and (b) have shown that, in contrast to previous beliefs, the Ross procedure can still be safely performed when the aortic valve malfunctions.

2. Underpinning research

Dr Robinson's research interests are in the development of statistical methodologies for tackling problems arising in engineering and medicine [see Section 3, R1–R6], with previous work on the optimal control of stochastic processes. He works with doctors in several hospitals in Britain (e.g. the Royal Brompton and Harefield NHS Trust, St Thomas' Hospital London, Aintree University Hospital Merseyside, the Royal Sussex County Hospital, Brighton) and in Germany (e.g. the Department of Cardiac and Thoracic Vascular Surgery at the University of Lübeck) on the design and analysis of medical studies.

Statistical analysis of data arising from cardiac procedures most often involves the development of survival and/or longitudinal models of the changing condition of a patient subsequent to a medical procedure being carried out. Survival modelling typically involves the separate modelling of short-term survival (e.g. using logistic regression) and long-term survival (e.g. using Cox regression). The analysis usually aims to determine the factors associated with longer survival, but other considerations may also be important. For example, comparing patients' survival with that of the general population, i.e. showing on a survival graph not only how patients in the study have fared but also showing the expected survival curve based on the national life table, matched by age and gender. Another survival comparison is with published survival curves based on earlier studies; bootstrap methods can be used to see whether these curves differ significantly from the current study.

Longitudinal data have usually been modelled using multilevel and mixed models adapted to the response being measured. Polynomial or piecewise linear models have been used for continuous measurements, while ordinal regression or Markov chain models have been used for ordinal measurements.

While Dr Robinson's many published research papers involve a large number of co-authors, mainly from the medical profession, he is solely responsible for the data-processing and the statistical analysis. All the research relevant to this case study has been carried out at the University of Sussex, where Dr Robinson has worked since 1989.

3. References to the research

R1 Sievers, H.-H., Stierle, U., Charitos, E.I., Hanke, T., Misfield, M., Matthias Bechtel, J.F., Gorski, A., Franke, U.F.W., Graf, B., **Robinson**, **D.R.**, Bogers, A.J., Dodge-Khatami, A., Boehm, J.O., Rein, J.G., Botha, C.A., Lange, R., Hoerer, J., Moritz, A., Wahlers, T., Breuer, M., Ferrari-

Kuehne, K., Hetzer, R., Huebler, M., Ziemer, G., Takkenberg, J.J.M. and Hemmer, W. (2010) 'Major adverse cardiac and cerebrovascular events after the ross procedure: a report from the German-Dutch Ross Registry', *Circulation*, 122(11 Suppl): S216–223.

R2 Hanke, T., Charitos, E.I., Stierle, U., **Robinson**, **D.R.**, Hemmer, W., Moritz, A., Lange, R. and Sievers, H.H. (2010) 'The Ross operation: a feasible and safe option in the setting of a bicuspid aortic valve?', *European Journal of Cardio-Thoracic Surgery*, 38(3): 333–339.

R3 Hoerer, J., Hanke, T., Stierle, U., Takkenberg, J.J., Bogers, A.J., Hemmer, W., Rein, J.G., Hetzer, R., Huebler, M., **Robinson**, **D.R.**, Sievers, H.H. and Lange, R. (2009) 'Homograft performance in children after the Ross operation', *Annals of Thoracic Surgery*, 88(2): 609–615.

R4 Hoerer, J., Hanke, T., Stierle, U., Takkenberg, J.J., Bogers, A.J., Hemmer, W., Rein, J.G., Hetzer, R., Huebler, M., **Robinson**, **D.R.**, Sievers, H.H. and Lange, R. (2009) 'Neoaortic root diameters and aortic regurgitation in children after the Ross operation', *Annals of Thoracic Surgery*, 88(2): 594–600.

R5 Hanke, T., Charitos, E.I., Stierle, U., **Robinson**, **D.R.**, Gorski, A., Sievers, H.H. and Misfeld, M. (2009) 'Factors associated with the development of aortic valve regurgitation over time after two different techniques of valve-sparing aortic root surgery', *Journal of Thoracic and Cardiovascular Surgery*, 137(2): 314–319.

R6 Hanke, T., Stierle, U., Boehm, J.O., Botha, C.A., Bechtel, M.F., Erasmi, A., Misfeld, M., Hemmer, W., Rein, J.G., **Robinson**, **D.R.**, Lange, R., Horer, J., Moritz, A., Ozaslan, F., Wahlers, T., Franke, U.F.W., Hetzer, R., Hubler, M., Ziemer, G., Graf, B., Ross, D.N. and Sievers, H.H. (2007) 'Autograft regurgitation and aortic root dimensions after the Ross procedure', *Circulation*, 116(11 Suppl): 251–258.

Outputs R1, R2, R3 best indicate the quality of the underpinning research. Outputs can be supplied by the University on request.

4. Details of the impact

The Ross procedure, introduced in the 1960s, involves the replacement of a failing aortic valve with the patient's own pulmonary valve. This procedure did not gain popularity until the late 1980s, when the technique for this operation was described in detail. The procedure became increasingly popular during the 1990s, and a registry of patients going under the Ross procedure was initiated. At this point, little was known about the long-term outcome of this procedure. However, in the early 2000s, the fallibility of the pulmonary implant started to become apparent [see Section 5, C1]. Dr Robinson's work on analysing data resulting from patients undergoing the Ross procedure dates back to 2000. The initial analysis, however, was based on data from the Cardiac Unit of the University of Lübeck alone, and was later extended to larger datasets. Around 2007, a group of physicians and researchers at Lübeck (Department of Cardiac Surgery, University of Lübeck, Germany) decided to address fears about the long-term success rate of the operation. This was motivated by two factors: (a) the widespread interest in this procedure in the early 1990s and (b) emerging good-quality data that could be used to provide a quantitative analysis of the success rate of this procedure in terms of the life expectancy and quality of life of patients undergoing this procedure.

Using data from the large patient population of the Dutch-German Ross Registry, Dr Robinson carried out a rigorous statistical analysis on 1,620 Ross-operated patients over a follow-up of 10,747 patient-years [R1, R2]. Dr Robinson's statistical analysis, and its interpretation by clinicians, showed that the outcomes using this procedure compared well with the outcomes of other approaches using artificial vales, and that the survival rate of adult patients following the operation was similar to the expected survival rate of the population.

In particular, the analysis confirmed that the autograft procedure is a valid option to treat aortic-valve disease in selected patients. Namely, the Ross procedure works well for young patients, and active people (e.g. sportsmen/women) who want to preserve their life quality by avoiding the daily use of anticoagulants. Moreover, the Ross procedure compares favourably for patients on dialysis [C2.2, C4 and C6], where the lifespan is reduced but there is an increase in life quality due to the avoidance of the regular use of anticoagulants. The result of Dr Robinson and his co-workers have contributed (a) to changes in the current practice guidelines of the European Society of Cardiologists [C2.1, C3 and C4 via C7] and (b) to reversing the negative impact of papers published in the 1990s on the Ross procedure. Dr Charitos commented that 'I believe our work has lead to a renaissance and reappreciation of the Ross procedure in the European area' [see C5 for relevant statistics].

5. Sources to corroborate the impact

Below are testimonies from physicians, with direct reference to the papers which Dr Robinson has co-authored and contributed to.

C1 David, T.E. (2009) 'Ross procedure at the crossroads', *Circulation*, 119(2): 207–209.

C2 **Professor Dr J.F. Matthias Bechtel**, Heart and Chest Clinic, University of Bochum.

One of the physicians involved (Dr J.F. Matthias Bechtel, now at the Heart and Chest Clinic, university of Bochum, Germany) says:

C2.1 'I also believe that the many manuscripts on the Ross-operation and the different ways it can be done contributed to the fact that, for example in the current practice guidelines of the European Society of Cardiologists, the Ross-operation is mentioned more detailed and positive than before. I believe the analysis of the Dutch-German registry contributed to this change'.

C2.2 'Today biological valves are preferred in dialysis patients; for years, mechanical valves were preferred because it was feared that there is an accelerated degeneration of biological valves in dialysis patients'.

C3 **Dr Efstratios I. Charitos**, Cardiac and Thoracic Vascular Surgery Clinic, University of Lübeck.

C4 The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) (2012) 'Guidelines on the management of valvular heart disease', *European Heart Journal*, 33: 2451–2496.

C5 The number of Ross procedures performed during the REF period shows an increase from a low of 87 in 1999 to a high of 144 in 2011 as given by the Ross Registry. See analysis of data in an email from Dr Charitos, dated 23 February 2013.

C6 Bechtel, T., Matthias, J.F., Detter, C. and Fischlein, T. *et al*. (2008) 'Cardiac surgery in patients on dialysis: decreased 30-day mortality, unchanged overall survival', *Annals of Thoracic Surgery*, 85(1): 147–53. Dr Robinson is acknowledged 'for expert statistical analysis and his kind advice when planning the study'.

C7 Takkenberg, J.J.M., Klieverik, L.M.A., Schoof, P.H., van Suylen, R.-J., van Herwerden, L.A., Zondervan, P.E., Roos-Hesselink, J.W., Eijkemans, M.J.C., Yacoub, M.H. and Bogers, A.J.J.C. (2008) 'The Ross procedure: a systematic review and meta-analysis', *Circulation*, 119(2): 222–228.