Institution: University of Glasgow
Unit of Assessment: 10 – Mathematical Sciences
Title of case study: Quantification of the benefits of statins in preventing cardiovascular disease

1. Summary of the impact

Cardiovascular disease is a major worldwide health issue and cholesterol has long been recognised as an important risk factor. The Robertson Centre for Biostatistics (RCB), led by Prof. Ian Ford, has played a central role in establishing for the first time the benefits of statins in preventing first-time heart attacks in men, with subsequent major influence on medical practice and guidelines for patient care. Innovative record linkage techniques used by the RCB have identified the long-term benefits of treatment, confirmed safety, and quantified the economic benefits.

2. Underpinning research

The Robertson Centre for Biostatistics (RCB) in the University of Glasgow was created in 1988 (as the Databases Unit) in order to structure existing research in the methodology and practice of biostatistics and to promote its development. Led by Ian Ford, Professor of Biostatistics, the RCB began in the Department of Statistics (now incorporated into the School of Mathematics & Statistics). In 2009, the RCB was recognised for its fundamental role in interdisciplinary medical research and moved to the Faculty of Medicine.

The RCB has been involved in many large and high profile studies but a particularly important example is the West of Scotland Coronary Prevention Study (WOSCOPS). Cardiovascular disease is a major cause of death worldwide and high cholesterol has long been implicated as a risk factor. However, in the late 1980's the effect of reducing cholesterol in patients who have not yet suffered any cardiac event, was unclear; indeed many thought that this could lead to increased risk of cancer and death. The WOSCOPS study sought to answer this question in individuals with raised cholesterol levels. The central role of the RCB and its statistical research are described below.

The conduct of the WOSCOPS study

As in any large clinical trial, statistical methods and expertise lay at the heart of the WOSCOPS study. This was essential in design, to meet the ethical demands of patient involvement and ensure the highest quality of statistical evidence. It was critical in the collection, collation and management of data to ensure information of the highest quality. It was central to the analysis and interpretation of the results, whose potential implications in terms of future patient treatment guidelines were enormous. The RCB was responsible for all of these aspects of the trial and for all subsequent publications. The complexity of the work involved in supporting trials is reflected in the size of the RCB, with approximately 50 staff, including 12 statisticians. The critical role of statistical methodology is indicated by the position of Ian Ford as one of the principal grant holders for the trials and as one of the principal authors in the subsequent publications in the highest ranking medical journals. Ford was the lead or corresponding author of all of the publications listed below. The adaptation of statistical methods to the complexities and scale of the WOSCOPS study was a fundamental and critical contribution to this interdisciplinary research. The results [2] provided the first definitive evidence of the link between cholesterol reduction and reduced risk of first-time heart attack and, importantly, established the safety of this approach.

Methodological issues in the construction and interpretation of statistical models

The complexities of large clinical trials need to be supported by methodological innovations. For example, the issue of whether statistical models to assess treatment effects should be adjusted for relevant covariates has been a controversial one in trial design and interpretation. Methodological work by Ford *et al.* [4] identified, in the context of Cox regression models, that adjusted and unadjusted models may not both be valid and that, even when they are, the model parameters may have different interpretations. This attracted significant attention, as a result of which a second paper [5] was invited by *Statistics in Medicine.* This indicated clearly, in a general setting of non-linear models, that when covariate adjustment takes place then change in the magnitude of treatment effects should be expected. The implications from a regulatory perspective that there should be a prespecified decision on whether inference should be conditional or unconditional with respect to covariates was clearly identified and the issues were specifically linked to the results of the WOSCOPS study.

Establishing record linkage as a valid and powerful means of follow-up

Clinical trials on the scale of WOSCOPS (involving an initial screening of 105,000 individuals) are large and complex operations which can usually be sustained for only a small number of years. The health effects of treatment may operate over much longer timescales and identifying the presence and nature of long-term effects is of major medical importance, but it is a major challenge to do this after the completion of a trial. In addressing this issue, the RCB has been a pioneer in the validation and use of computerised record linkage to identify the subsequent health history of trial subjects. Scotland is exceptionally well placed to exploit this approach as health information for patients across the whole country is collated centrally. Record linkage involves the matching of a unique identifier, or in the case of WOSCOPS patient information (such as name, date of birth, address), across different records, through a probabilistically constructed index. Ian Ford was corresponding author on one of the first validations of this approach [3] and supervisor of a University of Glasgow Statistics PhD thesis [4] which explored the effectiveness of the method in great detail. This established the suitability of health record linkage in Scotland for use in clinical studies and, in particular, it provided a valid mechanism for tracking the longer term health effects of cholesterol reduction in WOSCOPS patients [6].

3. References to the research

1) Shepherd J, Cobbe SM, Ford I, et al. (1995). Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. New Engl J Med. 333, 1301-7. doi:10.1056/NEJM199511163332001. Citations: 5128 (InCites), 6098 (Scopus) *
2) WOSCOPS Study Group (1995). Computerised record linkage: compared with traditional follow-up methods in clinical trials and illustrated in a prospective epidemiological study. Journal of Clinical Epidemiology 48, 1441-1452. doi:10.1016/0895-4356(95)00530-7
3) McLeod, M. (1995). *Record linkage applied to medical and cohort studies*. PhD thesis, University of Glasgow. (available from HEI)
4) Ford, I., Norrie, J. & Ahmadi, S. (1995). Model inconsistency, illustrated by the Cox proportional hazards model. Statistics in Medicine 14, 735-746. doi:10.1002/sim.4780140804
5) Ford, I. and Norrie, J. (2002). The role of covariates in estimating treatment effects and risk in long-term clinical trials. Statistics in Medicine 21 (19), 2899-2908. doi:10.1002/sim.1294 *
6) Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane PW, Cobbe SM: WOSCOPS Study Group (2007). Long-term follow-up of the West of Scotland Coronary Prevention Study. N Engl J Med., 357(15):1477-86. doi:10.1056/NEJMoa065994 *

* best indicators of research quality

4. Details of the impact

Evidence base for medical practice

The results of the WOSCOPS study represented the first demonstration of the benefits of statin therapy in a male population with no history of myocardial infarction, showing a 31% reduction in coronary events and a 28% reduction in deaths from coronary heart disease in patients taking pravastatin. A further major study, PROSPER (*Lancet* 2002; 23;360(9346):1623-30), also conducted by the RCB, established that taking pravastatin for an average of 3 years reduced the risk in an older population (70–82 years) where the epidemiological association between elevated cholesterol and increased risk is less evident. These studies therefore clearly established the evidence for statins as a primary prevention mechanism for reducing cardiovascular risk. The landmark nature of the WOSCOPS results is reflected in the subsequent very large number of medical citations.

Impact on health and patient care

Statins are now very widely used in primary prevention of coronary disease, with more than 60 million statin prescriptions dispensed in England alone in 2012. Although there have been other clinical trials which have investigated the use of statins in different patient groups with different risk categories, WOSCOPS remains the definitive study which first established the benefits, and safety, of statins in preventing first-time heart attacks for those with raised cholesterol. Indeed, there would be ethical issues in repeating a study of this type now that the benefits have been identified. WOSCOPS is therefore a primary source in the supporting evidence for national and international guidelines on the management of patients. Examples where WOSCOPS is cited include guidelines for risk estimation and the prevention of cardiovascular disease [a]. WOSCOPS is also extensively referenced in clinical aids such as *GPnotebook* (www.gpnotebook.co.uk), which assist doctors in decisions on suitable medications and management of patients.

At the international level, the American Association of Clinical Endocrinologists issued *Guidelines for management of dyslipidaemia and prevention of atherosclerosis* (2012) which recommends statins as the cholesterol lowering drug of choice, with the in-depth analysis of the treatment recommendations citing WOSCOPS as one of the major randomised controlled trials supporting the use of statins in primary prevention [b]. Similarly, the European Society of Cardiology/European Atherosclerosis Society issued *Guidelines for the management of dyslipaemias* (2011) which cites WOSCOPS to support the use of statins in patients who have been stratified according to cardiovascular risk and low-density lipoprotein levels [c]. The study has therefore had significant impact on patient care worldwide.

Identification of long-term health and economic benefits

A follow-up study of WOSCOPS patients 10 years after the end of the trial showed continuing effects in risk reduction and no long-term safety concerns. This study, conducted by the RCB, integrating record linkage, statistical methods and economic analysis, shows that treatment of 1000 patients for five years in middle age saves over 1800 days in hospital over the following 15 years, with a consequent saving to the NHS of £710k [d]. As the use of statins has increased internationally, the replication of these effects over large populations clearly represents savings of enormous size, both in financial terms and in the positive improvement in patient health. The use of record linkage has therefore had the double impact of providing a highly effective and cost-saving means of pursuing medical follow-up studies in general, as well as identifying the long-term health and economic impact associated with the original WOSCOPS study in particular.

Public understanding and debate

The recent, record linkage based, follow-up study of WOSCOPS patients [d] has attracted significant press coverage [e], reflecting the widespread public interest in the associated health and economic issues. The study has therefore contributed significantly to public understanding and public debate of the underlying issues. A recent example was the reference to WOSCOPS long-term follow-up as an excellent illustration of the potential of record linkage in medical research at the national launch of the new Health e-Research Centres (HeRCs).

5. Sources to corroborate the impact

Evidencing impact on health and patient care

[a] Risk estimation and the prevention of cardiovascular disease, Scot. Inter. Guidelines Network, Guideline 97, 2007. ISBN 1899893997. http://www.sign.ac.uk/pdf/sign97.pdf

[b] AACE guideline, 2012 https://www.aace.com/files/lipid-guidelines.pdf ; WOSCOPS, PROSPER: p40 (Tables 18 and 20, major trials in primary prevention), pp. 28 and 29.

[c] ECS guideline, 2011 http://eurheartj.oxfordjournals.org/content/32/14/1769.full.pdf; WOSCOPS (*NEJM* 1995, ref 19) and PROSPER (ref 26), Table 3, pg 1780.

Evidencing identification of long-term health and economic benefits

[d] McConnachie A, Walker A, Robertson M, Marchbank L, Peacock J, Packard CJ, Cobbe SM, Ford I. (2013). Long-term impact on healthcare resource utilization of statin treatment, and cost effectiveness in the primary prevention of cardiovascular disease: a record linkage study. *Eur Heart J* ; doi:10.1093/eurheartj/eht232

Evidencing influencing public understanding and debate

[e] The Herald (9 July 2013): Giving statins to middle-age healthy men saves money
The Scotsman (10 July 2013): Statins for heart problems could save NHS millions
Daily Express (10 July 2013): Give statins to healthy Scots now
Reuters (19 July 2013): Statins for healthy men may save money: study