



Lowrie, Richard (2012) *A cluster randomised controlled trial of Pharmacist-led Statin Outreach Support in Primary Care*. PhD thesis.

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**A cluster randomised controlled trial of Pharmacist-led
Statin Outreach Support in Primary Care**

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BSc Hons (First Class)

**Submitted in fulfilment of the requirements for the degree of PhD
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April 2012

Dedications

To Rosemarie.
And Frances, Monica, Joseph, Michael and Thomas.

In memory of Stevenson bhoy. Through the mercy of God, rest in peace. Amen.

To my parents.

Summary

Background

Elevated blood lipids (particularly cholesterol and sub-fractions) contribute to the risk of developing cerebral, peripheral and cardiovascular disease and associated complications which are leading causes of morbidity and death.

Statins reduce the risk of suffering vascular events, with or without decreasing cholesterol levels. Statin prescribing continues to increase but there is scope to improve prescribing and dosing, particularly in primary care. However, there is insufficient empirical evidence to inform approaches to quality improvement.

Methods

Following pilot work, we designed a new model of primary care based pharmacist-led intervention for General Practitioners (GPs) and nurses. The aim of the intervention (called Statin Outreach Support, SOS) was to improve statin prescribing by GPs, in line with recent evidence, targeting patients at highest risk of suffering a vascular event.

Eleven trained pharmacists worked in SOS allocated practices one day per week for a year. During this period, the pharmacist met three times with all GPs, all nurses and other practice staff. Between meetings, pharmacists used patient level clinical and prescribing data to identify eligible patients and help practices initiate, up-titrate the dose or switch to simvastatin 40mg where indicated.

The effectiveness of SOS was tested in a prospective single blind cluster randomised controlled trial.

Usual care (UC) practices received no pharmacist support during the study.

With a mean of 1.7 years follow up, the study had over 90% power (at 5% significance) to detect a difference of 12% in the proportion of patients with controlled cholesterol after practices had received the SOS intervention.

Results

Thirty one practices were recruited from the UK's largest Health Board area. At randomisation, 16 practices were allocated to the SOS intervention and 15 to UC with 4,040 patients included at baseline. Recruited practices showed few differences compared with invited, non participating practices. Practices and patients randomised to each arm of the study had similar distributions with respect to age, complications, cholesterol levels and statin prescribing. The mean age was 68 years; 53% male, 45% ischaemic aetiology. Fifty nine percent had no statin prescribed at baseline; only 51% had cholesterol controlled.

Follow up included 7586 patients in 29 practices (one practice had disbanded between recruitment and randomisation and another practice dropped out). Compared with UC, the SOS intervention achieved the primary endpoint of increasing the proportion of patients prescribed Simvastatin 40mg with controlled cholesterol (SOS 44.9% vs. UC 27.9%; odds ratio 1.79 (95% CI: 1.61, 1.98), $p < 0.001$). Secondary endpoints were also improved in the

SOS arm practices. The intervention effect was strong and consistent across most subgroups including a positive impact on patients from practices in areas of greater socioeconomic deprivation.

Conclusion

A pragmatic, new, complex intervention was developed, tested and shown to be effective in a cluster randomised controlled trial with good internal and external validity.

If implemented on a wider scale, in practices with comparable characteristics and baseline prescribing, the SOS intervention has the potential to reduce the burden of vascular events for patients with vascular disease.

This work provides a convincing evidence base for the role of pharmacists collaborating with primary care practices, to improve statin prescribing and drug based cholesterol management, for patients at highest risk of suffering vascular events.

Acknowledgements

Thank you to my supervisors Jill Morrison and Alex McConnachie.

Thank you to the team of 11 pharmacists who delivered the intervention: Victoria Hunt, Jan Currie, Fiona Allen, Lynn King, Dinesh Soni, Janet Black, Marjorie McGhie, Noreen Downes, Chris Johnson, Alia Gilani, Sheila Tennant.

Thank you to Brian Rae for his wizardry in helping to make this happen.

Thank you to Clare Mackie for the initial spark, all those years ago.

Declaration

With the exceptions of collect the data and deliver the intervention, I declare that I have done every single bit of the work described in this thesis (with Jill's and Alex's advice and help).

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Publications and presentations

Re: thesis

Lowrie R, Morrison J, McConnachie A. (2010). A cluster randomised controlled trial of pharmacist-led Statin Outreach Support (SOS) in primary care: design and baseline characteristics. *Contemporary Clinical Trials* 31:303-311.

Lowrie R. (2010). “Statin Outreach Support: Methods and baseline characteristics” Presentation to the conference of the Scottish School of Primary Care. Perth (Scotland), 21- 23 April.

Lowrie R. (2011). “Can pharmacists improve Statin prescribing and cholesterol control, by providing educational and organizational support in primary care?” Presentation to the 9th International Conference on Coronary Artery Disease. Venice, Italy. 23 - 25 October.

Re: related work

Lowrie R, Mair FS, Greenlaw N, Forsyth P, McConnachie A, Richardson J, Khan N, Morrison D, Messow M, Rae B, McMurray JJV. (2011). The Heart failure and Optimal Outcomes from Pharmacy Study (HOOPS): rationale, design and baseline characteristics. *Eur J Heart Fail* 2011;13: 917-924.

Lowrie R, Mair F, Greenlaw N, Forsyth P, Jhund P, McConnachie A, Rae B, McMurray JJV. (2011). Pharmacist intervention in primary care to improve outcomes in patients with left ventricular systolic dysfunction. *Eur Heart J* doi:10.1093/eurheartj/ehr433.

Lowrie R. (2011). “Pharmacist Intervention to prevent hospitalization and death in patients with heart failure: a prospective cluster randomised controlled trial.” Presentation (‘Late Breaking Clinical Trial’) to the American Heart Association Conference. Florida, North America. 12 – 16 November.

Abbreviations

ADP	Adenosine Diphosphatase
CABG	Coronary Artery Bypass Graft
CHD	Coronary Heart Disease
CVD	Cerebrovascular disease
CRP	C - reactive protein
DM	Diabetes Mellitus
DNA	Deoxy-ribo Nucleic Acid
eGFR	estimated Glomerular Filtration Rate
G	Group (practice)
GG&C	Greater Glasgow and Clyde
GMS	General Medical Services
GP(s)	General Practitioner(s)
HPS	Heart Protection Study
HDL	High Density Lipoprotein Cholesterol
LDL	Low Density Lipoprotein Cholesterol
LTC	Long Term Condition
MI	Myocardial Infarction
NO	Nitric Oxidase
PDGF	Prostaglandin Generating Factor
PVD	Peripheral Vascular Disease
QOF	Quality and Outcomes Framework
SH	Single Handed (practice)
SOS	Statin Outreach Support
TIA	Transient ischaemic attack
UC	Usual Care
UNICEF	United Nations International Children's Federation
vs.	Versus
WHO	World Health Organisation

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Chapter 1

Introduction

1.1 Primary Care

In the 1978 Alma Ata Declaration, primary care was described as constituting the first element of a continuing health care process (WHO 1978) and more recently, 'Now More Than Ever' (WHO 2008) reaffirmed the central importance of a strong primary health care system as a means of tackling the epidemic of chronic conditions. A key aspect of primary care described by the declaration was the delivery method being reliant on good teamwork, with the most recent report describing the primary care team as a "hub of coordination" (WHO 2008). This included the involvement of "outside partners" e.g. housing, employment. Primary care is regarded as an essential and cost effective component of a health system (Starfield 1994).

The importance of preventive medicine, the contribution of essential drugs and the increase in noncommunicable disease were acknowledged. The increase in the number of people in developing and industrialised countries with Long Term Conditions (LTCs) such as heart disease and the challenge of individuals presenting with multiple illnesses was recognised.

These references to teamwork and preventive medicines underscored the potential for the pharmacy profession to make a meaningful contribution to primary health care.

1.1.1 Primary Care in the United Kingdom and the policy context for teamwork

While there have been numerous health care reforms and changes in delivery between and within different countries over the past 50 years, the UK has retained the National Health Service (NHS) model. It was established in 1948 as the first publicly funded, comprehensive health system.

When the NHS began, general practice was often perceived to be of low quality. Since then, however, general practice and primary health care delivery has shifted from single handed GPs working in isolation to a multidisciplinary team based model which brings advantages in terms of co-ordination and comprehensiveness. Effective teams improve the quality of primary care from the perspective of patient, organisation and team members. However, many teams fail to work together for complex reasons. In this context, together with a general trend of shifting responsibility, workload and resources from acute care to primary care, healthcare professionals' roles have evolved. Expansion of professional roles, opportunities afforded by skill mixing and professional substitution have contributed to the evolution of primary care teams. Relentless changes in the way the NHS delivers primary care has led to more emphasis on joint working within teams, with the locus of control remaining within primary care general practices.

One of the main policy drivers in this context included 'Primary Health Care – an agenda for discussion' (Department of Health and Social Security, 1986) which expressed the need for the development of working teams and asserted 'Primary health care is best provided when family doctors, community nurses and practice nurses work together as members of a primary care team'. 'Promoting better health' (Department of Health and Social Security, 1987) changed the structure of the contract which GPs had with the NHS, requiring greater

concentration on health promotion and the prevention of disease. Practices began to involve nurses as salaried employees, in different roles within the practice, to support delivery of contractual obligations. 'Working for patients' (Department of Health 1989) facilitated GPs to expand and innovate further. GP fundholding was introduced and, with this, innovation and increased opportunities for inclusion of different professional groups in practices e.g. physiotherapists, pharmacists. Practice nurses' roles began to diversify.

1.1.2 Opportunities for pharmacists in general practices

This diversification, albeit restricted to practices with fundholding status, led to opportunities for pharmacists to deliver bespoke services aimed at improving prescribing. Prescribing was acknowledged as an area of high cost with scope for improvement. In 1996, during fundholding, and for the first time in the UK, some pharmacists became salaried Practice employees, working within Practice teams. The author was one of the few clinical pharmacists to work in Glasgow general practices at that time, following pioneering work by Clare Mackie, which confirmed the contribution of medication review by pharmacists for patients receiving multiple medications (Mackie 1999).

At that time, the remit of many general practice based pharmacists was to review patients' medicines with full access to relevant clinical records and, if indicated, with patient and then GP agreement, modify them in line with evidence of cost effectiveness and quality improvement. Patients targeted for review were those receiving polypharmacy and were often prescribed expensive medicines. The objectives of the medication review included improvement in the quality of care through prescribing improvement and maximisation of cost effective prescribing and use of medicines. At that time, a lack of empirical evidence existed to justify medication review as a means of reducing hospitalisations or impacting on mortality. Since then, the evidence base around this form of pharmacist-led support has developed and some variants of medication review have become established practice. However, some reports have described a lack of convincing evidence of long term benefit on morbidity/mortality endpoints, suggesting the evidence base could be improved (Holland, 2007).

Other models of pharmacist-led prescribing support which did not involve direct patient-facing activity were described, with short term improvements in prescribing, but studies have not considered longer term outcomes (Oxman 1995; Davis 1995).

In 1997, the Labour government initiated major changes in the organisation of the NHS with the White Paper 'The New NHS: Modern, Dependable' (Department of Health 1997) which signalled the end of the 'internal market' concept. Fundholding was replaced with an ethos of co-operation. This government policy paper, with a focus on the efficient use of resources, also encouraged teamwork in primary care to help meet the increasingly complex needs of service users. To enable this change, interdisciplinary learning involving different healthcare professionals was promoted as a way forward (Leathard 1994). A subsequent systematic review concluded that more research was required to demonstrate whether and how this approach impacted on professional practice (Cooper 2001).

Now, over 10 years later, primary care groups and trusts have been replaced by health and social care partnerships. The General Medical Services contract is in place, incentivising evidence based prescribing for specified LTCs (Roland 2004). Pharmacists' opportunity to

support prescribing in primary care by working collaboratively with GPs has continued to grow in response to increases in the number, diversity and availability of preventive medicines for LTCs (NHS Executive, 1999).

1.1.3 Drivers for primary care prescribing support

Since the inception of the NHS, organisational change has been constant. Efficiency savings are now the key driver for change, which is not surprising given the current level of expenditure on healthcare and the global economic situation (Ramesh, 2010).

Quality improvement together with improved patient safety is also high on the NHS agenda, with delivery mechanisms such as clinical governance and audit supporting implementation. Improving prescribing is seen as an important means of delivering quality improvement and achieving cost effective use of resources. For example, statins reduce the risk of vascular events if prescribed appropriately for targeted patients but they account for a large item of expenditure: in 2000, statins cost NHS Glasgow £5.5million per year. Since then, the cost of statin prescribing has increased to approximately £20 million per year, and there are cost savings to be made by choosing to prescribe Simvastatin instead of other, equally efficacious alternatives.

1.2 LTCs

A LTC is a condition that “requires ongoing medical care, limits what one can do, and is likely to last longer than one year” (World Health Organisation (WHO) 2005). Managing LTCs has been described by the WHO as “the health care challenge of this century”. Approximately 78% of healthcare resources are directed towards the care of people with LTCs.

1.2.1 The prevalence of LTCs

Major health gains experienced in recent years coupled with increasing advances in treatment and prevention, have resulted in the majority of people living longer lives. For example, the population in Scotland is both ageing and declining: the proportion of Scots aged over 65 is predicted to increase from 15.9% in 2001 to 26.6% in 2031. Estimates from the Scottish Health Survey report show that in 2003, 26.5% of adults in Scotland reported a long standing illness, disability or infirmity which limited their activities in some way. A further 14.7% reported LTCs that were not limiting. Both increased markedly with age, particularly the proportion of adults in the oldest age group (over 75 years) (Scottish Health Survey 2003). As there is an association between increasing age and risk of developing a chronic condition, the proportion of households containing someone with a LTC showed an increase from 30% in 1999 – 2000 to 33.8% in 2005 - 2006 (Loretto 2007).

1.2.2 Co-morbidities and polypharmacy

Many patients with one LTC can remain relatively stable over the long term. However, it is estimated that up to 45% of patients suffer from more than one condition (National Public

Health Service for Wales 2001). Patients with multiple LTCs have healthcare costs that are six times higher than patients with only one condition, with the cost of repeat medicines forming a part of this (Naessens 2011). Medicines are used extensively by patients who have LTCs because medicines can help delay or prevent the onset of conditions worsening e.g. Beta Blockers reduce the risk of recurrent myocardial infarction, preventing the onset of associated illness, loss of function and costs associated with treating symptoms and preventing complications. As the number of conditions suffered by an individual increases, so does the number of medicines and therefore, the need for prescribing decisions to be based on sound evidence of effectiveness and efficiency.

1.2.3 Polypharmacy and determinants of care management

Several ‘disease management models’ aim to reduce the impact of LTCs. Many of these acknowledge the importance of recognising that when a person is prescribed polypharmacy for multiple co-morbidities, it may be an indicator of the need for the provision of more intensive care. The Castlefields model is a disease management model which stratifies the population at risk by a number of factors, one of which is polypharmacy (Lyon 2006). Polypharmacy often arises from co-morbidities and patients with co-morbidities are estimated to use a disproportionate amount of healthcare resources (Yu 2003). Polypharmacy is thought to be an independent risk factor for elderly people falling and in patients with heart failure, polypharmacy (or the number of co-morbidities) may predict worse outcomes. These examples, and the pressure to prescribe cost effectively, suggest that effective models of prescribing support in primary care would be useful.

1.3 Prescribing in Primary Care

An overview of the history and the processes involved in repeat prescribing gives an insight to potential ways to improve prescribing effectiveness and efficiency. As with many interventions in primary care, prescribing support models are likely to be complex. To be effective, support may need to target and influence different parts of the repeat prescribing process e.g. the GPs’ choice of drug and patient attendance at the practice for prescription collection. It is recommended that complex interventions require extensive piloting before testing in a randomised controlled trial (Medical Research Council 2011).

1.3.1 Long term and repeat prescribing

In Primary Care, drugs are the most common intervention for LTCs with up to 75% of patients receiving a prescription on consulting their GP (Soumerai 1990; Bligh 1992). Over the past 50 years there has been a steady increase in the availability and range of medicines. In response, the proportion of NHS expenditure allocated to pharmaceutical products has continued to rise, with estimates suggesting primary care prescribing accounts for over 80% of the cost of all medicines and 10% of the total NHS budget (National Prescribing Centre Resource Document, 1999). Much of the volume increase stems from increasing numbers of people with LTCs receiving repeat prescriptions (prescriptions issued from a general practice computer using a repeat prescribing program, enabling supply of medicines within a given time period). In the United Kingdom over 30 years ago, the proportion of repeat prescriptions was estimated

to be around 25% of all prescribed items. Twenty years later, it had increased to about 75% of all prescribed items (Diikers 1977; National Prescribing Centre Resource Document, 1999). In 1996, one quarter of the population received some form of repeat medication, increasing to 90% of people aged over 75 years (Harris 1996). Repeat prescriptions represent about 80% of the cost and 70% of the volume of prescribing in general practice (Audit Commission 1994; National Audit Office 1992).

In the elderly, the volume of repeat prescribing, appropriateness and time requirement to review appropriateness have long been regarded as a concern (Anderson 1980; Tulloch 1981; Nicol 1984; Freer 1985). The true extent to which inappropriate prescribing occurs is unknown because of limitations associated with lack of agreement on objective measures of appropriateness, publication bias, and uncertainty about the context of prescribing decisions. Available reports indicate that inappropriate prescribing is mostly detectable through the use of drug doses above recommended limits (Buetow 1996; Buetow 1997). However, experience suggests 'inappropriate' prescribing should (in most cases, while appreciating the heterogeneity of patients) encompass sub-optimal use of medicines of known benefit, or sub-optimal doses in comparison with guideline recommendations.

Sixty six percent of prescriptions in primary care are issued as repeats, with no face to face contact between patient and GP (The Audit Commission 1994; The National Audit Office 1993; Sykes 1996). GPs are reported to have difficulty protecting the time for an annual review (McGavock 1999; Zermansky 1996). During a review, it is recommended that the efficacy, appropriateness, adverse effects, interactions, value for money, the patient's understanding of the treatment and compliance are all evaluated within the confines of a consultation (The Audit Commission 1994). Repeat prescribing can lead to excessive amounts of waste medicines (Zermansky 1996).

Over and above the growth of LTCs, other reasons for the increase in repeat prescribing include: drugs causing habituation and dependence e.g. some analgesics, hypnotics or anxiolytics; improved detection and management of patients through screening; availability of new medicines for primary, secondary and tertiary prevention and societal and attitudinal changes towards diseases and medicines taking. With the advent of the GMS contract Quality and Outcomes Framework in 2004 (which coincided with the start of the intervention tested in this study) there has been a shift of practice towards evidence based management of diseases including the provision of financial incentives to prescribe statins for patients with vascular disease (QoF achievement Data 2005). Annual review of repeat prescribing for patients receiving four or more medicines is included in this annual review (BMA and NHS employers 2011). The review incentivises and encourages critical examination of the ongoing appropriateness of repeat prescribing.

1.3.2 Support for long term prescribing

A balance needs to be struck between introducing new, evidence based medicines and maintaining patients on existing, well tolerated medicines. The benefits of introducing a new medicine might not outweigh the benefits of maintaining the status quo at an individual patient level. Ideally, each patient would receive a review of their medicines and conditions, in order that options can be discussed and changes made if required. Pharmacist-led 'Prescribing Support' can offer additional capacity to offer review of prescribing (NHS Executive 1999).

Recognition of the need to improve evidence based prescribing and minimise variation in prescribing formed part of the rationale for introduction of the General Medical Services Quality and Outcomes Framework in 2004 (Roland 2004).

Many other objectives are potentially achievable through prescribing support:

- Minimisation of iatrogenic hospital admissions, particularly for those with polypharmacy and the elderly (Tully 1991; Lindley 1992; Gosney 1984; *Medical Expenditure Panel Survey* 2001);
- Minimisation of prescribing costs by encouragement to prescribe the least costly medicine when therapeutic equivalents are available e.g. in 2007, it was estimated that if Simvastatin was used instead of alternative statins for 10% of patients, this would generate £84.7M savings in England alone (Department of Health 2007);
- Ease GP workload, by providing an annual medication review (MacRae 2003);
- Reduce variation in prescribing outcomes (Carthy 2000).

1.3.3 The prescribing knowledge – practice gap

In relation to health related interventions including prescribing, there is often a failure to implement research findings (*Effectiveness Matters* 1998). Many recognised barriers are entirely rational e.g. patients or GPs deciding not to implement on a case by case basis, because circumstances differ from the trials upon which the evidence is based. These departures from the evidence base are common and account for much of this gap between research and practice (David 2003; Mair 1996; Sudlow 1997; Mashru 1997). However there are many other barriers to implementation of evidence based medicine and an associated range of theories on how to improve dissemination and implementation of research findings (Grol 1997, Fraser 2003) which could be applied at the individual or health care system level (Smith 2003).

Discussions on the implementation of evidence based medicine have acknowledged factors influencing prescribing. These include GPs' knowledge, professional experience, role perception of GPs, time pressures (patient and GP), patient expectations, patient demand and the number of GPs in a practice. An understanding of these has illuminated the processes shaping GP prescribing decisions (Carthy 2000; Watkins 2003; Webb 1994; Britten 1997, Cockburn 1997). According to Haynes (2002), clinical decisions should consider evidence based medicine at the individual patient level. They describe a four part model:

1. Ascertainment of what is wrong with the patient and what treatment options are available;
2. Consideration of options informed by research evidence concerning the efficacy, effectiveness and efficiency of medicines when this is available;
3. Consideration of the patient's preferences;
4. Application of clinical expertise to bring these considerations together and communicate the decision with the patient.

Anticipating specific barriers to implementation of the research evidence on a particular topic can inform solutions. Barriers are likely to vary depending on the practice, GP and patient's circumstances. Finding out what the barriers are, before devising well intentioned solutions

may be the best way forward (Haynes 1998). There are many reasons why the evidence based model of prescribing is not followed. Failure to take the patient's beliefs and preferences into account during a consultation might reduce the likelihood of agreement on an evidence based choice. Known difficulties in the process of effective communication of the benefits and risks of any particular treatment cannot be underestimated (Veldhuis 1998; McColl 1998; Freeman 2001; Sweeney 1998).

1.4 Pharmacy in the NHS and Primary Care

1.4.1 Pharmacy

The Royal Pharmaceutical Society of Great Britain was incorporated by a Royal Charter granted on 18th February 1843. A Supplemental Charter was granted on 19th November 1953 in which the Council of the Society was agreed to have the function, for the benefit of the public, to be more appropriately equipped to:

- regulate the members;
- lead the strategic development and policies of the profession of pharmacy;
- support the science and practice of pharmacy;
- engage with the wider public debate on health related matters and on the role of pharmacy in contributing to the health of the public.

In a 2007 White Paper named 'Trust, Assurance and Safety', there was a commitment to separating regulation from professional leadership in all health professions. In response, the Royal Pharmaceutical Society separated into two new organisations during 2010: the General Pharmaceutical Council, which regulates the profession, and a new professional leadership body, which focuses on supporting the needs of members. Members are those who have registered as pharmacists in Great Britain, having completed and passed a 4 year degree or masters degree in Pharmacy at an approved University, then completed a further pre-registration placement for 1 year in practice and passed a pre-registration examination. In 1992 it was estimated that the cost of training a pharmacist was at least £25,000 (The Royal Pharmaceutical Society 1992).

1.4.2 Pharmacy roles in Primary Care

In response to the mass manufacture of pre-packed patented and generic medicines over the past 20 years, pharmacists have spent less time compounding and preparing medicines. In parallel, increases in the prevalence and incidence of LTCs, together with increases in the number of available medicines has led to an increase in prescribing choices, volume and cost. This created a need for additional support to prescribers. Pharmacists' ability to influence prescribing grew, including being able to independently prescribe. A more developed clinical focus in undergraduate courses, and policy shifts encouraging teamwork enabled these developments.

As the cost of prescribing spiralled, some pharmacists' roles moved from dispensing to supporting the management of prescribing. This move involved forming better links with practices, focussing on repeat prescribing and minimising waste. Increased capacity to

undertake these new roles was facilitated by a move to enable suitably trained counter assistants and dispensers in community pharmacy, to dispense and supply prescriptions. It could be argued that another stimulus for pharmacists applying their skills and knowledge within general practices was, and continues to be, the lack of opportunity for clinical career development or systematic opportunity to apply undergraduate and postgraduate clinical training within the community pharmacy environment.

From the pharmacy workforce census in 2008 (www.rpsgb.org.uk/pdfs/census08.pdf) there were 43,845 registered pharmacists living in the United Kingdom with 82.8% in active employment. Community Pharmacy was the largest sector of practice with 71% of those actively employed working in this sector (23.1% of whom were registered as locums). There were over 15,000 community pharmacies in the UK. These were private for profit organisations with some income coming from NHS remuneration through prescription dispensing. Many were owned by contractors who owned multiple chains of pharmacies. Approximately 21% of pharmacists worked in Hospital pharmacy. Most of the remaining 8% operated as NHS employees in Primary Care, providing strategic prescribing guidance or based in general practices, supporting prescribing directly through patient interaction. The general practice based role is most commonly described as 'Prescribing Support Pharmacy'. Numbers working in this sector are not available; it is probably the most recently established branch of the profession in relation to employment in Primary Care.

1.4.3 Policy context for clinical role expansion

The first policy recommendation for the expansion of new clinical roles came from the Nuffield report (Nuffield foundation 1986). Since then, opportunities have arisen for pharmacists to work within general practices, initially as prescribing advisers alongside medical prescribing advisers. In England, there were 50 prescribing advisers in 1991 and as the need evolved, numbers rose to 250 in 1998 (*Prescribing Advisers: an update* 1999). No additional information on workforce figures in primary care prescribing advice could be found after this period. Because of their few numbers, roles were necessarily strategic, working at a distance from practices, at regional level, supporting the achievement of rational prescribing targets through the provision of prescribing summaries and prescribing advice to practices.

Around this period, pharmacists began to work within general practices. The opportunity arose from a demand from some practices for clinical medication review / repeat prescribing support. Inter-professional learning was facilitated. Some pharmacists became salaried employees in General practices. Pharmacists were found to generate savings in practices' drugs bill by reviewing patients receiving polypharmacy and cutting back on the number of medicines or changing expensive medicines to less expensive but equally efficacious alternatives. Pharmacists also helped implement clinical evidence, acting as expert therapeutic advisers. The White Paper "Primary Care: the future" reinforced this move, consolidating Government interest in the potential for pharmacists to become more integrated into primary health care teams and medical practices. The paper noted that "regular attendance by pharmacists in surgeries would lead to greater understanding of drug use by patients and more effective use of drug budgets by GPs" (National Health Service Executive 1996). Since then, several other white papers have endorsed the view that pharmacists have a valuable contribution to make in patient care although none have cited an evidence base to substantiate this (Secretaries of State for Health, Scotland and Wales 1996a). Innovation and removal of

barriers to further development were encouraged. More inter-professional cooperation to provide services relating to prescribing and greater mixing of skills was promoted.

From within the Pharmacy profession, the move towards clinical application of pharmacists' skills and knowledge was supported albeit slightly belatedly. In 1997, The Royal Pharmaceutical Society's 'Pharmacy in a New Age' strategy developed the concept further (Royal Pharmaceutical Society of Great Britain 1997), reiterating the consensus that pharmacists, by virtue of their undergraduate training, were expected to know more about drug treatment than any other professional (McCreedy 1997). However, to become expert in the clinical use of drugs requires regular initiation and monitoring of the drugs together with the honing of relevant knowledge and skills. These pre-requisites were available to pharmacists working in general practices. For the majority of pharmacists working in community pharmacies, most of their working hours were spent in a dispensary, checking the accuracy of prescriptions before issue to patients, counselling patients on management of minor ailments without access to clinical records. The skills and knowledge maintained through this core role may lead to an unrivalled awareness of the names, strengths, manufacturers and indications of commonly available medicines. The status of the clinical conditions of patients presenting with prescriptions and their demographic variables, co-morbidities and relevant medical histories remain largely unknown to most community pharmacists, making it difficult for most community pharmacists to develop an expertise of drugs in use.

In 1999, in an editorial, the *Pharmaceutical Journal* said 'Supply is, of itself, no longer an adequate role for the 21st century pharmacist' indicating that pharmacists were still requiring encouragement to establish and extend their clinical role, ten years after the idea was first mooted (Parkin 1999).

The 2003 Health and Social Care act enabled primary care organisations to contract with the private sector for the provision of pharmaceutical care services (Pollok 2005) and the NHS Pharmaceutical Care services regulations (2005) allowed community pharmacists to provide a range of services e.g. anticoagulant monitoring.

More recently, the need for greater involvement of pharmacists as part of the multidisciplinary team has surfaced again (*A report on the future of the NHS in Scotland* 2005), some 20 years since the concept of multidisciplinary team working was advocated in the WHO declaration of Alma Ata. These policy drivers recommended 'Shifting the balance of care' from medical to team based models, a better community based preventive focus, aiming to reduce secondary care and primary care health service utilisation in favour of better self management in the community, improving medicines management and involving pharmacy to a greater extent (particularly in relation to LTCs).

1.4.4 Evidence base for pharmacists adding value to LTC management

There are few examples of long term trials demonstrating improved morbidity or mortality outcomes from pharmacists collaborating with primary care providers. One reason for this may be the difficulties inherent in measuring and valuing benefit from the complex interventions delivered by pharmacists as they collaborate with other healthcare professionals. Another reason may be the choice of patients in most trials of medication review. Patients have tended to be recruited on the basis of their polypharmacy and therefore multiple co-

morbidities, rather than their ill health. Patients who are more seriously ill or clinically unstable are often excluded, which may make it more difficult to demonstrate changes in clinical outcomes. However there are some disease areas such as hypertension, diabetes and heart failure where multidisciplinary input (including pharmacy support) is recommended, due to evidence of usefulness in terms of prevention of hospitalisations or intermediate outcomes (Carter 2009; McAlister 2004). Heart failure is the only example of a LTC where a systematic review has confirmed the utility of pharmacists working collaboratively (with GPs and other healthcare providers (Koshman 2008) rather than independently e.g. based in community pharmacies, where lack of access to relevant clinical information may limit impact (Holland 2007a).

In reducing the risk of recurrent falls in the community dwelling elderly, medication review by pharmacists appears to be synergistic with other interventions (Gillespie 2004).

These positive findings have largely been shown in the context of trials involving medication review delivery by few, specialist pharmacists, collaborating within specialist teams. When pharmacists involved in trials are non-specialist, or the interventions are characterised by a lack of formal collaboration within a team, outcomes are generally neutral (Holland 2007a, Holland 2008, Lowrie 2011). Nevertheless, the prevailing view does not differentiate between pharmacists with different levels of knowledge and skills (NHS Executive and National Prescribing Centre 1996). However, there is some evidence of a positive impact on prescribing changes by non specialist, community pharmacists. This includes a systematic review of community pharmacists' interventions for patients with established coronary heart disease (Watson 1998; Blenkinsopp 2006), improvement in anticoagulant control (Hall 1995), smoking cessation (Blenkinsop 2003; Maguire 2001), emergency hormonal contraception (Anderson 2009), cholesterol lowering (over the short term, through patient-facing interventions) (Gardner 1995; Tsuyuki 2002), and blood pressure control (Blenkinsopp 2000).

When the focus is on improving CHD treatment appropriateness or reducing future risk of cardiovascular death through a multifaceted intervention for patients with CHD, Community pharmacists have not yet demonstrated a significant impact on long term clinical or surrogate clinical outcomes (Community Pharmacy Medicines Management Project Evaluation Team 2007; Pharmacy Practice Research Trust 2009).

1.4.5 Adoption of clinical roles by Community pharmacists

One factor limiting the move of more pharmacists from supply / dispensing into clinical domains has remained constant throughout the years: the need for a pharmacist to be present in registered pharmacy premises to supervise the dispensing and supply of medicines. While this ruling is currently under review, a pharmacist is still professionally required to be present at all times when medicines are dispensed. This limits the movement of community pharmacists into practices, to deliver more clinical services, during regular working hours. Another limiting factor is the lack of progress in the transfer of clinical (diagnostic, test results) information between pharmacies and practices, which is an important factor in clinical and prescribing decision making. A large proportion of locums (The 2005 Pharmacy workforce census (Hassell 2006) found that locums represent over a third (37%) of all community pharmacists) may create additional difficulties for continuity of care and repeated contact with patients, both of which are important to monitor effectiveness and safety of

changes to medicines in primary care. A further (untested, fundamental) factor is whether patients and practices would be supportive of the concept and practicalities involved in community pharmacists delivering part of their chronic disease management on a shared basis between pharmacists and GPs.

Meanwhile, community pharmacists are adapting to changing population demographics by expanding their roles to include advice on dispensed and over the counter medicines and self care. Community pharmacists have developed procedures for triaging: information gathering when responding to requests for advice that identify when the presenting problem can be managed within the pharmacy and when referral for medical advice is needed. A major policy shift supports this move – with the belief that costs are less and quality of care better if health professionals focus their efforts on prevention. There is growing emphasis on the pharmacist's role as 'first port of call' in response to symptoms. This forms the core of a new contractual arrangement for pharmacists in Scotland (Scottish Government 2010).

In parallel with these developments, the five year pharmacy undergraduate degree course includes a greater focus on improving students' understanding and application of therapeutics.

1.4.6 What has changed in pharmacy practice for patients with LTCs?

In spite of all the policy drivers, organisational changes, shift in population demographics and disease burdens, the core functions for the majority of community pharmacists has remained: to safely provide medicines and advice to the public within registered premises. At present, pharmacists with clinical aspirations to prescribe and modify treatments for patients with LTCs working within Community Pharmacies remain few in number. There are likely to be proportionately more general practice based pharmacists applying their clinical skills e.g. prescribing, than community pharmacists.

A new community pharmacy contract is operational in Scotland and the rest of the UK, with opportunities created for the delivery of clinical pharmacy skills and knowledge to improve the management of LTCs. However, at present, the majority of remuneration remains linked to prescription volume rather than introducing prescribing quality improvements or cost savings.

Better long term evidence of effectiveness and efficiency would help underpin developing Pharmacy roles in community pharmacy and in general practice. As General practice based pharmacists' roles are established and access to relevant clinical information is secured, it therefore makes sense to evaluate this model of care, to generate empirical evidence of impact and shape evidence based policy. Models of general practice based prescribing support will now be described.

1.5 Overview and origins of pharmacist-led GP prescribing support in Primary Care

1.5.1 'Rational' prescribing and support

Acknowledging variations in prescribing practice and that some prescribing decisions are more appropriate than others, the term 'rational prescribing' was introduced (Gilley 1994). It articulates the aim of ensuring "appropriate, safe, effective and economic" use of medicines

(Parish 1973) with some observers suggesting the aims should take into consideration the patient's quality of life (Barber 1995). 'Prescribing support' was therefore described as professional support to one or more of the components of the prescribing process, aiming to promote high quality, cost effective medicines use (Department of Health 1998).

As expected from a process involving many inputs there are large variations in the extent and nature of prescribed medicines within and between practices. For example, variations in statin prescribing are well recognised, with studies explaining up to 20% of the variation (Packam 1999; Majeed 2000; Gibson 2002; Bradshaw 1999; Ward 2007). Contributing factors include the prevalence of CHD, patient level deprivation and a combination of nitrate prescribing and age between 35 and 74 years. The assertion that up to 80% of patients consulting with their GP have common conditions that could be treated with similar medicines (Audit Commission 1994) remains unproven.

Prescribing support is indicated from a fiscal perspective. Factors contributing to a growth in drug expenditure include increases in spend on disease prophylaxis, high cost/new products for previously untreatable diseases, increased expectations from the public and media together with innovative marketing strategies from the pharmaceutical industry. All of these pressures lead to a greater need (or perceived need) for rational, cost effective prescribing. While GPs are independent contractors, NHS resources are used to pay for prescribing, which highlights the importance of the economic dimension (Avorn 1992; Panton 1993; Beard 1998).

Programmes of prescribing support are intended to increase the rational use of medicines. Rational use should lead to decreased costs and improvements in the quality of care. The best case scenario is when both of these issues are addressed simultaneously, but it is difficult to choose a prescribing topic and prescribing support method which does both. There are examples of prescribing support initiatives that improve quality of care but increase costs, (Kreling 1989) and cost reduction programmes that lead to poorer quality of care (Bloom 1985). One report found practice level pharmacist prescribing support to be cost effective, compared with no prescribing support, in the context of a controlled trial (Rodgers 1999). If prescribing support achieves stated aims it may provide a means of reducing the lag time between publication of clinical evidence and implementation of that evidence in practice (Burrell 1990; *Getting evidence into practice* 1998).

1.5.2 Strategic prescribing advice

In the late eighties and nineties, the responsibility for managing and financing prescribing budgets was devolved from some Health Boards and Health Authorities to practices, in a move to improve efficiency. Fiscal policies and incentives were introduced to bring about rapid change e.g. the Indicative Prescribing Scheme was introduced into the UK in the early 1990s (Bligh 1992).

Professional prescribing advisers were introduced, to raise awareness and communicate key messages on prescribing preferences. Those carrying out the role were medically or pharmaceutically trained. Their roles focussed on the promotion of rational, cost effective prescribing advice to GPs. Their approach to changing prescribing practice included meeting with GPs to discuss areas of prescribing, highlighting prescribing variation between practices and encouragement for practices to conduct prescribing audit. Practices' prescribing trends

were summarised by the prescribing adviser (there was often a 3 – 6 month lag time in the availability of this information) and shared with the practice in advance of the meeting.

Evaluation of the impact of this model of prescribing support is lacking, perhaps because a key part of the role aimed to raise awareness rather than effect direct change. Prescribing advisers were based outwith practices and delivered strategic, general advice, without accessing patient level information. Therefore, only the GPs in the practice were aware of reasons for prescribing and their practice population's demographics and health needs. This asymmetry of important background information possibly limited the relevance of the advice offered by the traditional prescribing advisers' role.

Methods adopted by prescribing advisers included many of the approaches known to be of variable effectiveness at bringing about prescribing change. These included facilitation of educational meetings, production of local bulletins, and passive dissemination of prescribing reports (Audit commission 1994). From available evaluation of the strategic prescribing advisory role, there is a lack of convincing evidence of effect (Harris 1984; Braybrook 1996; Newton –Syms 1992). However, the absence of evidence may not imply evidence of absence, because for many prescribers, a third party drawing attention to variations between their practice and that of others may have been a strong stimulus to change.

1.5.3 Models of prescribing support

Approaches to prescribing support have evolved in response to the changing needs of patients, GPs, the evidence base for management of targeted conditions and financial constraints. Service evaluations have shed some light on the apparent effectiveness of different models of prescribing support delivered by primary care pharmacists (Wilson 1997; Jesson 1997; National Prescribing Centre and NHS Executive 1998; Squires 1997; National Health Service Executive 1996). However, due to a lack of adequate description of roles and methodological rigour in evaluation, much of the available published work has not clarified which models of support are effective and efficient. Inadequate design, lack of a control group, poorly defined interventions and an emphasis on process related outcomes limit the generalisability of findings and have led to a call for more rigorous comparative effectiveness research in this area (Beney 2004).

1.5.4 Prescribing Support at practice level: prescribing support pharmacists

Recognising the potential for improvements in patient care and prescribing efficiency through direct support to GPs, additional investment was made to deliver complementary prescribing support at GP, patient and practice level. This move aimed to bring about effective prescribing change together with cost savings, in addition to encouraging GPs to prescribe in line with the evidence. Better collaborative working between medical and pharmaceutical professionals was encouraged and Prescribing Support pharmacists were introduced into general practices. Methods included working in practices, with full access to patients' medical and prescribing information at practice level, to ensure prescribing advice was tailored to practices' and patients' needs. This also helped translate prescribing decisions based on guideline or formulary advice into action at patient level.

There were some calls for more practice based pharmacists, because anecdotal evidence suggested they were able to reduce prescribing costs (Wells 1997; Wells 1998; Department of Health and NHS Institute for innovation and improvement 2007). Others have asserted that there are many ways to reduce prescribing costs without involving prescribing support pharmacists (Tant 1999).

The methods adopted by General practice based pharmacists were diverse. So too are the terms used to describe the role. These have included “GP pharmacist” (Kempner 1996), “primary care pharmacist” (Marinker 1994) “clinical pharmacy service” (*Who should provide a clinical pharmacy service to primary care?* 1996) and “consultant or freelance pharmacist” (Powell 1997). By default, the role involves a pharmacist working with medical practitioners and others in the practice team. The core objective is to identify, with the practice, areas of prescribing in need of attention or support. The pharmacist gains agreement on how best to support the area of prescribing and bring about change. Methods include modification of prescribing mediated through presentations and patient or practice level reports, prescribing or clinical audits. All approaches aim to influence GPs, nurses or patients directly. Success is measured by cost saving, better adherence to clinical guidance or both. Being closer to the prescribing process also means that evaluation of impact was immediate: within 1-2 months of introducing or encouraging a prescribing change, a shift in prescribing could be detected through a search of the practice’s repeat prescribing on the practice computer system. This acted as a useful reinforcement to support subsequent prescribing change.

6. Prescribing Support models

The introduction of general practice based pharmacy prescribing support started during the GP fundholding era, when ‘early adopter’ practices contracted work on a sessional basis from freelance pharmacists or from NHS contractor pharmacists with a special interest in the clinical use of drugs in Primary Care. As Pharmacy led prescribing support models have evolved over the past 15 years, general descriptions of their characteristics, costs and benefits have appeared (National Prescribing Centre and NHS Executive 1998; Kempner 1996; Powell 1997). The roles are not practised exclusively by pharmacists although the pharmacy profession has led the description (Jesson 1999). Overall, the quality of evaluation varied and as is often the case with innovations in health care delivery, questions of reproducibility, effectiveness and value for money remained unanswered (Soumerai 1990; Soumerai 1989; Haaijer-Ruskamp 1995).

There are few scientifically rigorous studies of the effectiveness of prescribing support models other than medication review, in Primary Care. They appear as a subset of the larger body of research involving educational and other interventions that aim to change health professionals’ behaviour (Thomson 2002; Oxman 1995; Davis 1995). One review of evidence on the impact of pharmacists providing a prescription review and monitoring service in primary care suggested improvement in patients’ clinical status and suggested reduced prescribing costs, while acknowledging the need for further research to confirm these findings (Tully 2000). The NHS Centre for Reviews and Dissemination subsequently disagreed with the authors’ suggestions of the likely effectiveness of pharmacists’ prescription review and monitoring activities, but agreed on the need for future research in this area. Further, the NHS centre recommended more independent and blinded outcome assessment, use of comparison groups

and appropriate statistical analysis in future research (NHS Centre for Reviews and Dissemination 2004).

1.6.1 Requirements for the delivery of prescribing support

There is no agreed guidance on the minimum skills and knowledge of pharmacists who are asked to deliver Prescribing Support roles. However, the training needs of pharmacists to deliver clinical support to patients within general practices and bespoke training programmes have been described (Webb 1998; Sykes 1997). These include developed clinical, analytical and communication skills, for pharmacists with no prior experience in the clinical use and review of drugs (Speak 1998).

However, as might be expected for any developmental role, the nature of the working relationship and the conditions of employment varied, as did tenure and remuneration. In most cases, the pharmacist was recognised as a member of the practice staff, attending the practice on a full or part time basis, regularly e.g. one day per week (Lacey 1998). In Glasgow, the norm was (and remains), for pharmacists to work in the same practice, one day per week.

An adequate description of prescribing support aims and key models is important, as this enables appraisal of effectiveness. Therefore, the remainder of this chapter draws on available literature and some personal experience of the following prescribing support models delivered in the UK over the past 15 years:

- Pharmacist-led clinical medication review;
- Passive dissemination of prescribing information;
- Prescribing audit, analysis and feedback;
- Prescribing formularies;
- Academic detailing / educational outreach.

The model described as ‘educational outreach’ or ‘academic detailing’ will be considered fully in Chapter 2 and subsequent chapters, because of all the above, it is the model most closely aligned to the new model developed and tested in the trial described in this thesis.

1.6.2 Pharmacist-led clinical medication review

1.6.2.1 Definition and delivery

Clinical medication review is a process where ‘a person with knowledge of medicines reviews the patient, their medicines and their clinical diagnoses during a consultation’ (Mackie 1999). Clinical medication review usually takes place during a face to face consultation. It involves evaluating the therapeutic efficacy of each prescribed or ‘over the counter’ drug, eliciting the patient’s unmet (medicine related) needs and minimising costs associated with prescribing. Other issues such as adherence, potential adverse effects, interactions and the patient’s understanding of their conditions and treatment are considered during the consultation. Another definition comes from the Task Force on Medicines partnership and the National Collaborative Medicines Management Services programme “a structured critical examination of a patient’s medicines with the objective of reaching an agreement with the patient about

treatment, optimising the impact of medicines, minimising the number of medicine related problems and reducing waste” (Medicines Partnership and The National Collaborative Medicines Management Services Programme 2002). From experience in Glasgow, it commonly takes place in the general practice or patients’ home, lasts up to an hour, depending on the complexity of the case and the pharmacist’s skill and knowledge set. Pharmacists are ideally placed to conduct medication reviews because it demands a combination of drug based clinical and technical knowledge of prescriptions and the prescribing process. It is valued by the NHS because it is thought to save money and improve the quality of prescribing (NHS Executive 1999). Although not necessary, access to full medical records and a face to face consultation with the patient is preferred, because there appears to be an evidence base in favour of accessing these data, and / or the collaboration that brings (Holland 2007b, Koshman 2008).

When a medication review aims only to detect and reduce waste from repeat prescribing, there may not be any need for a consultation with the patient, nor any need to access medical records, and no need for a pharmacist with additional skills and knowledge of the clinical use of medicines. When a consultation takes place, the review has been described as a ‘Brown Bag review’ because patients were posted an appointment with an empty brown bag enclosed, then asked to put all their medicines inside the bag and bring it along to discuss with the pharmacist at an appointment in the practice. The main part of such a review is a reconciliation of prescribed versus supplied medicines. Evaluation of this type of review led to estimates of 500 tonnes of medicines wasted in England every year, worth approximately £100 million (Gilles-Burness 1999).

1.6.2.2 GP and patient views of medication review

GP views on medication review are generally favourable, with the following benefits described by GPs who have had exposure to the service: improved prescribing practice, raised standards of patient care and patient satisfaction, increased GP knowledge and confidence, decreased workload, better multi-disciplinary working and communication (MacRae 2003a). It is popular with patients because it creates the protected time to ask questions about treatment (MacRae 2003b).

1.6.2.3 Medicine reviews in context

In view of the epidemic of LTCs (WHO 2005) and poor compliance with medicines (Haynes 2008), medication review is seen as an important component of the broader issue of medicines management (the processes aiming to ensure medicines are used effectively). In the UK, as part of the National Prescribing Centre, the Medicines Management Services Collaborative has focussed on repeat prescribing systems and medication review as key areas for improvement (Medicines Management Services Collaborative 2001). The need for clinical medication review has entered into policy documents e.g. the National Service Framework for older people proposed that patients over the age of 75 should have their repeat medicines reviewed annually and those on 4 or more medicines twice yearly (Department of Health 2001). Medication reviews are currently remunerated within the GP contract Quality and Outcomes Framework (QOF) (The NHS Confederation 2002). However, a relatively superficial review is incentivised through the QOF; it does not require the patient to be

engaged directly. Instead, the review can be paper or computer based, without patient involvement.

1.6.2.4 Effectiveness of polypharmacy medication review

There is good evidence from randomised controlled trials to support the effectiveness of pharmacist-led medication reviews for patients receiving polypharmacy. Effectiveness has been measured as the identification and resolution of drug related problems, improved compliance, better adherence with prescribing guidance, reduced need for GP consultations, improved patient knowledge of medicines or a reduction in polypharmacy and cost (Zermansky 2001; Mackie 1999; Krska 2001; Granas 1999; Forrest 1999; Petty 2001; Jameson 1995). When effectiveness criteria have included other endpoints e.g. prevention of hospitalisations, clinical events or delaying mortality, medication review is not yet proven (Holland 2007; Lowrie 2011).

1.6.2.5 Collaborative disease management clinics

When reviews are targeted at subgroups of patients with particular LTCs, outcomes appear more favourable (Suksomboon 2002; Soorapan 2002; Peterson 2004). However, as anticipated with any complex intervention evaluation, differences in the intervention characteristics and the organisational context in which the intervention is delivered have a bearing on efficacy. A recent systematic review underscored the importance of context in relation to pharmacists' activities for patients with heart failure (Koshman 2008). Pharmacist directed care (pharmacist initiated and managed medication review with little or no integration with the team based approach) was found to be less effective than pharmacist collaborative care (medication review as part of a multidisciplinary team approach). Collaboration appeared to enhance the effect of pharmacists' reviews for patients with heart failure (Gattis 1999; Triller 2007; Rainville 1999) and this finding is consistent with collaborative, team based review and intervention to prevent elderly, community dwelling people falling (Zermansky 2006; Keys 2004; Kannus 2005; National Osteoporosis Society 2002; Marsh 2003; American Geriatrics Society 2001; Hill-Westmorland 2002).

Descriptions of the medication review process (duration, intensity, number of contacts per patient, training and experience of each pharmacist) and the healthcare environments in which the studies took place (primary/secondary care or at the interface, across different healthcare systems) are sufficient to enable generalisation of the results. Over time, outcomes have changed from numbers of drug related problems identified and resolved to hospitalisations prevented. This shift possibly reflects the medication review model gaining in maturity together with a growing need to demonstrate added value in terms of reduced hospitalisations for people with LTCs.

Lessons from these observations include:

- The importance of capturing drug, intermediate clinical e.g. cholesterol or blood pressure readings, and health service utilisation outcomes if possible;
- Careful choice of the patient population;

- A clear description of the nature, intensity, duration and organisational context in which the intervention takes place;
- An evaluation of the costs of delivering the intervention and impact on medication adherence;
- Collaborative working and capturing, describing and valuing the contributions of the wider healthcare team;
- Focus on a topic of importance, where there are recognised shortfalls in the quality of care;
- Providing an intense intervention with long enough duration to achieve behavioural change.

If more attention is given to these features, the chances of a longer term, positive impact is more likely. It is also important to pre-specify any anticipated unintended consequences in testing a new intervention; not many of the trials reported this. These features are likely to apply equally to the new intervention described and tested in this thesis.

1.6.3 Passive dissemination of prescribing information

Unsolicited, passive dissemination of printed educational material is characterised by a lack of targeting of the message or assessment of the educational needs of the recipient. The approach is thought to be relatively ineffective as a means of changing healthcare professionals' behaviour according to a Cochrane Review on the subject (Freemantle 2005). While there were only 11 studies fitting the criteria for inclusion in the review, evaluation of their combined impact was impractical because of the poor reporting of results and inappropriate primary analyses.

Much of the research in this area relates to the dissemination of prescribing guidelines, or clinical guidelines ('systematically developed statements to assist practitioner decisions about appropriate healthcare for specific clinical circumstances') (Institute of Medicine 1990).

Passive dissemination of prescribing guidelines may act to raise awareness which may help pave the way for change at an individual level (Soumerai 1990; Denig 1990; *Implementing clinical guidelines: can guidelines be used to improve clinical practice?* 1994). However, some individual studies indicate that there is no significant change in GP's attitudes and knowledge following direct mailing of consensus statements (Hunnskaar 1996) or guiding prescribing decisions e.g. prescribing of antibiotics for acute conditions (Schaffner 1983). Davis reviewed the literature on different forms of prescribing support and concluded that commonly used methods of delivering education, such as conferences, have only limited impact on improving professional practice (Davis 1995).

Of direct relevance to this thesis is the finding that publishing and distributing national guidelines on cholesterol management (focussing on the use of statins and dietary measures), does not appear to have contributed to changing doctors' approaches to management (Sempos 1993). However one report suggested that a simple, passive educational intervention can change prescribing behaviour, compared with feedback and education (Schectman 1995). In addition, it is thought that the publication of major trials heralding a significant shift in prescribing trends may lead to changes in prescribing (Muhammad 2001). Muhammad investigated whether the publication of three landmark statin trials were associated with an

increase in the market share of statins in Canada and found a study specific effect, post trial publication. However, the strength of this evidence was weak: their study lacked a control group and did not account for confounding.

It stands to reason that strategies most likely to change practice are those which are actively communicated, underpinned and shaped by behavioural change and adult learning theory (Foy 2001).

It should be remembered that conferences, presentations and distribution of clinical guidelines may not aim to change professional practice. Instead, they may aim only to increase awareness of a particular topic, which in turn may create a better starting point for introduction of more active dissemination strategies to facilitate change, at some point in the future. In fact, there is some suggestion that the distribution of bulletins through post or email is a low cost approach and any small effects may be worthwhile in the long run (Soumerai 1986). One study in North America showed passive dissemination, in addition to educational outreach, improved marginal cost effectiveness (Soumerai 1986). The principle of combining different models to achieve a more powerful effect is analogous to the collaborative approach described in studies of medication review, and will be used in the intervention described in this thesis.

Another prescribing support model combining passive dissemination with more tailored approaches is the use of postal prompts to GPs, for named patients. In a London based study, Feder et al trialled this approach, to improve cholesterol measurement together with the prescribing of Beta Blockers and statins, for patients who had recently been discharged from hospital after a coronary event. Their intervention increased the proportion of patients attending for cholesterol checks at their practice but failed to improve prescribing (Feder 1999).

1.6.4 Prescribing audit, analysis and feedback

In general, published audit work in healthcare settings has focussed on standards of clinical practice or diagnostic performance rather than prescribing (Mugford 1991; Buntix 1993). Prescribing audit is the systematic, critical analysis of the quality of prescribing. It does not make inferences about the quality of life for the patient, but it can be used to estimate the population level impact of evidence based prescribing choices. For example, prescribing of angiotensin converting enzyme inhibitors (known to be effective and cost effective for heart failure due to left ventricular systolic dysfunction) may vary significantly across different practices. If the practices have similar demographics and access to effective services, then excluding any other justifiable reasons for the difference, prescribing audit enables recognition of what is feasible and a starting point for improvement.

The Cochrane Collaboration assessed the effects of audit and feedback on healthcare professionals' prescribing and patient outcomes. They found it to be effective, but only moderately so. One interacting factor consistently shown to predict the effectiveness of prescribing audit across studies was baseline non-compliance with recommended prescribing (absolute effects likely to be greater) (Jamtvelt 2005). This might be expected, because there may be more scope for change if the starting point is lower.

Practice level summary and analysis of prescribing data has been used to compare the prescribing of medicines between general practices, but the impact requires to be evaluated beyond the short term and include a comparator group (Harris 1993). Prescribing audit creates an opportunity for discussion and feedback on the reasons for prescribing variance and departures from 'best' practice. One study showed it to be effective and more efficient than educational outreach (Anderson 1996).

Prescribing audit is a useful means of differentiating between established and best practice. In some cases, raising awareness of these differences during a face to face meeting may be sufficient to trigger a change in prescribing, but evidence is lacking for this effect. Perhaps the best approach is to combine it with several other models, again, to reinforce the communication of a message, in much the same way that multidisciplinary teams work together to achieve a more pronounced effect than uni-professional, solo efforts. One evaluation of prescribing audit delivered by community pharmacists (who worked on a sessional basis within General practices) showed cost savings and reported improved levels of communication and co-operation between GPs and community pharmacists. GPs also felt that the quality of the meetings was superior to other local postgraduate events (Pilling 1998).

'Prescribing indicators' are now in common use across the UK. These are derived from prescribing audit and are set thresholds of prescribing of targeted medicines e.g. the least expensive bisphosphonate from the available options sharing the same indication. While opinions vary as to the suitability of some indicators (Asworth 2002), if a practice achieves their indicator threshold, a payment is triggered. This incentive to the practice is smaller than the savings generated as a result of the change in use the drug under question. While there is very little empirical evidence of the impact of such schemes on quality improvement, they are known to change prescribing, in the same way as evidence based prescribing for targeted LTCs has improved as a result of financial incentivisation through the new GMS contract (Roland 2004).

Overall, there are few scientific assessments of the effectiveness of prescribing audit, and significant variation in the nature, intensity and delivery mechanisms, thus limiting transferability of the model as a tool for prescribing support. However, there may be merit in combining this with other approaches. As an example of this, Eccles showed that routine attachment of educational reminder messages by reporting software or coloured stickers (in addition to audit and feedback) was effective in changing radiology referrals (Eccles 2001). This study highlights one of the difficulties in evaluating studies of audit and feedback: describing the intervention and context sufficiently to enable appraisal.

1.6.5 Prescribing formularies

Formularies are a limited range of medicines for specified conditions. The medicines are chosen on the basis of clinical evidence of relative efficacy and relative cost. The main reasons for using formularies are to promote rational prescribing and limit costs (Jolles 1981; Reilly 1989; Greenfield 1982; Department of Health 1990; Harding 1985; McGavock 1990) Formularies are designed to encourage the uptake of more effective prescribing (clinically and economically). They are also seen as a mechanism for quality improvement in general practice (Roland 1998).

A systematic review concluded that there is insufficient robust evidence to justify the use of formularies per se, or involvement in their development, as an effective model of modifying prescribing behaviour (Pearson 2003). Methodological weaknesses limited the usefulness of the authors' conclusions. One report (only available as a supplement) described the use of "closed formularies" (a tighter list of options restricting choice to a bare minimum with non formulary prescribing disabled through computerised restrictions) combined with several other approaches e.g. academic detailing, and reported effectiveness (Sbarbaro 2001).

1.6.6 Academic detailing (Educational Outreach)

The original published account of "academic" detailing can be traced to a paper by Avorn and Soumerai in 1983 and then seven years later (Soumerai, Avorn 1990). The authors described in detail a technique for influencing prescribing behaviour and applied it across four states in North America in a randomised controlled trial. 'Detailers' (pharmacists with additional, clinical and communication skills), met with physicians in their workplace to communicate 'balanced, unbiased prescribing information'. The physicians were targeted because of their high use of apparently inappropriate medicines. The magnitude of the impact of the model was highly significant (14% reduction in prescribing of targeted drugs compared with controls; $p = 0.0001$) compared with other studies of prescribing change. A comparable reduction was seen in drug costs (however a full cost effectiveness analysis was not conducted). The effect persisted for nine months after the start of the intervention. Since then, many investigators have tried variants of this model with different degrees of success.

An 'outreach visit' is a term used to describe a personal visit by a trained professional to a health provider in his or her own practice, to improve the practice of health care professionals. (Braybrook 1996; Newton-Syms 1992). Several therapeutic areas have been targeted for change through outreach visits, and simple issues generally can be influenced through single visits to practices (Braybrook 1996; Newton-Syms 1992; Ekedahl 1994). It follows that more complex or multiple issues relating to prescribing may require more than one outreach visit or exploration of reasons for current prescribing practice, before any attempt is made to influence change through a single visit. However, the content, context, nature of the outreach visit, duration, training of the professional providing the support or the characteristics of the GP receiving the support are not well described. A Cochrane Review of the effects of outreach visits on health professional practice or patient outcomes commented on their promising effects, but stressed the need to ascertain the key characteristics of outreach visits that are important to success (Thomson 2002).

The views of physicians receiving the intervention are not well chronicled: one report could be found in abstract form only, which related to work done in UK nursing homes by Boardman in 1999. GPs and nursing home staff who received the programme reported that it was well received with nearly half of those GPs mentioning that it had directly influenced their prescribing. Overall the programme was viewed as important and useful (Boardman 1999).

A new model of prescribing support could try to incorporate the theoretical principles described by Mullen and Cooper in their review of educational interventions (Mullen 1985; Cooper 2001). However Davis suggested that there are difficulties inherent in linking research findings to theories of behavioural change (Davis 1995).

Combining the learning from evaluation of educational outreach with learning from other prescribing support models, it would make sense for NHS pharmacists delivering outreach to diagnose practice and GP level barriers to prescribing change. These barriers (described in more detail in Chapter 2) can originate from the GP, practice organisation e.g. approach to call/recall, patients or prescribing guidance. As clinical practitioners with access to patient level information and experience reviewing patients' medicines in primary care, practice based pharmacists can understand and empathise with GPs and practice nurses in the reasons why the evidence is not always implemented. Different barriers are likely to arise in different practices; therefore separate strategies could be used to address these barriers. Combinations of prescribing support models appear more effective than more simple models, and the lack of clear evidence of which models are effective, suggests the need to generate a new model by combining existing approaches, define it, pilot it then test it.

An in depth review of the evidence for and against educational outreach/detailing is covered in Chapter 2, together with distillation of the implications for research and description of how the lessons learned have been incorporated into the SOS intervention model and trial.

1.7 Therapeutic uses of statins in vascular disease

Optimal drug based management of cardiovascular disease is important because it can reduce the risk of clinical events and delay early death. The management of dyslipidaemia has an important role in the reduction of these risks. Statins have revolutionised dyslipidaemia management and in the process, reduced the risk of morbidity and mortality in patients with coronary, cerebrovascular and peripheral vascular disease (Scandinavian Simvastatin Survival Study Group 1994; Sacks 1996; LIPID study group 1998; Shepherd 1995; Downs 1998; Heart Protection Study Collaborative Group 2002). The mean reduction in cholesterol was 25%, which resulted in clinically significant benefit. Contra-indications are limited to active liver disease, pregnancy and breast-feeding.

Simvastatin is regarded as the treatment of choice in the secondary prevention of CHD within the UK population (Phillips 2000). Generic simvastatin is the least expensive and can achieve cholesterol control in the vast majority of patients, if prescribed at 40mg daily dose (HPS, Scandinavian Simvastatin Survival Study Group (4S) 1994). In terms of spend; statins represent the largest drug cost to the NHS (£738 million in 2004). It has been estimated that using simvastatin instead of more expensive alternatives e.g. Atorvastatin could save the NHS £1.1 billion over 5 years (Moon 2006) without any detrimental effects. In Primary Care in Glasgow during 2005 there were more than 600,000 prescriptions for statins at a total cost of over £12 million; one fifth of which could be saved if simvastatin was used instead of the other prescribed statins. If a new approach to improving statin prescribing can be introduced, cholesterol levels at the individual level are likely to decrease. In the longer term (at 3 - 5 years after daily use of a statin) clinical events are likely to become less frequent in those treated. If 19 patients with vascular disease (Appendix III) receive a statin (e.g. simvastatin 40mg for 5 years) then it is likely that one major vascular event e.g. a myocardial infarction, will be prevented irrespective of the extent to which cholesterol levels are reduced.

As a result, many clinical guidelines have summarised these findings with a view to changing prescribing practice accordingly.

1.7.1 The basis for clinical guidance on statins

Prevention of atherosclerotic vascular disease requires control of all known risk factors e.g. smoking, hypertension, and glucose control. No single risk factor, including cholesterol level, should be viewed in isolation. While support for health related behavioural change (e.g. obesity, diet, physical activity, alcohol) should be offered at population and individual level, attention has focussed on statins, because they are more effective and efficient at reducing cholesterol and have the greatest measurable impact on clinical outcomes. The pathogenesis of atherosclerosis and the mechanism of action of statins are described in Appendix I.

It is known that many more patients than those currently treated, could benefit from statins if they were offered them. However, resources are finite and in an example of the law of diminishing returns, benefits diminish as the estimated risk of suffering an event decreases. Trials which included patients at highest risk (i.e. with the highest end point rate in the placebo control arm) showed the greatest absolute risk reduction. For practical and economic reasons, the use of statins is therefore recommended only for patients who are at high risk and set to gain most.

For patients who do not have any evidence of established vascular disease, the aim is to prevent the onset of a first coronary event e.g. heart attack. This approach is called primary prevention and emphasis is given to identifying patients at high-risk of developing atherosclerotic vascular disease, as they obtain greater benefit from treatment with a statin. A coronary event rate of 30% at 10 years (i.e. 3% per year) has been advised as the threshold for treatment. It is now recommended that risk stratification should be carried out using the Joint British Societies' 'Cardiovascular disease Risk Prediction Charts' (British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association 1998) (Appendix II). This is the tool recommended by the Scottish Intercollegiate Guidelines Network (SIGN; Guideline 40). Cardiovascular disease risk takes account of the risk of stroke in addition to coronary heart disease risk for primary prevention.

Secondary prevention includes patients with established vascular disease (coronary artery bypass graft (CABG), MI, Stroke, IHD, TIA, Angioplasty and peripheral vascular disease) and those with diabetes aged 40 years or above. All these groups should be offered a statin regardless of cholesterol concentrations, a recommendation based on the Heart Protection Study (HPS) (HPS Collaborative Group 2002). Appendix III describes the respective risk categories for each subgroup, derived from the HPS and Chapter 2 describes a critical appraisal of the HPS. It was felt to have the greatest implications for immediate changes in clinical practice, and therefore, previous guidelines (UK, European and North American - Appendix IV) were updated in the year following publication of the study.

This sudden change in recommended prescribing practice created the opportunity to test a novel intervention aiming to improve the use of statins in line with the new guidance, for those at greatest risk.

1.7.2 The need for better statin prescribing

In response to growing acknowledgement of the benefits, their prescribing has increased more dramatically than most other medicines (Ramsay 2006; Bull 2003). However, this generates three linked questions:

1. Of those with established vascular disease, are all eligible patients receiving a statin at the right dose? If not, what can be done to improve uptake of adequate prescribing and dosing?
2. Can pharmacists based in practices turn their attention to improving uptake, through a model of prescribing support?
3. Can this work be adequately described and tested, to ensure a robust answer to these questions?

Based on the review of prescribing support models described above, there are no ‘off the shelf’ interventions to ensure maximal uptake of statin prescribing guidance. This argues for innovation in the design and application of a novel intervention, the testing of which forms the focus of this thesis.

1.7.3 The need for better evidence of (Pharmacy led) improvements to prescribing

Primary care needs more implementation research because of the variability in uptake of robust clinical evidence and the negative impact on effectiveness and efficiency of patient care resulting from this (Foy 2001). To date, qualitative research involving GPs has improved our understanding of possible reasons why clinical evidence may not translate into practice (Veldhuis 1998; McColl 1998; Freeman 2001; Sweeney 1998). Together, these reports and others (Hemminiki 1975; Avorn 1982; Bradley 1991; Virji 1991; McGavock 1993; Britten 1995) suggest:

1. A wide range of factors have been shown to influence the prescribing decision making process and many of these are independent of the acceptability or availability of clinical evidence;
2. The evidence based model cannot be assumed to be robust;
3. Practical issues e.g. time constraints to learn about new evidence and systematically apply it in practice, limit the application of some evidence-based prescribing guidelines.

Therefore, in devising a prescribing support model, these points should be addressed.

1.8 Could educational outreach help improve statin prescribing?

There is a recognised need to evaluate the effectiveness of outcomes from outreach visits in terms of clinical outcomes whenever possible (Thomson 2002). If this is not possible, surrogate clinical outcomes could be used, particularly in cases where there is a robust link between clinical outcomes and the surrogate end point e.g. HbA1c, blood pressure, cholesterol levels. A strong link exists between cardiovascular, cerebrovascular and peripheral vascular morbidity/mortality and the use of statins (Scandinavian Simvastatin Survival Study Group 1994; Sacks 1996; LIPID study group 1998; Shepherd 1995; Downs 1998; Heart Protection

Study Collaborative Group 2002). Educational outreach appears to be a promising way of delivering quality improvements in prescribing, but at present, there is insufficient evidence to enable routine application as a means of improving prescribing beyond 1 year, improving statin prescribing and clinical or surrogate clinical outcomes. Reasons for this include:

- Inadequate description of the components of interventions;
- Inadequate description of training and qualifications of those delivering the model;
- Lack of pragmatic endpoints other than prescribing
- Unknown efficiency;
- Lack of generalisability of existing evidence;
- Weaknesses in choice of methodology and analysis.

1.9 The need for this research

Pharmacists working in general practices provide education, counselling, drug use review and non dispensing services. The effectiveness of these services has been investigated for many years, but most studies in the field have been of poor quality e.g. only 23 of 104 studies reviewed in 1993 by Hatoum and Akhras included a control group (Hatoum 1993). Morrison and Wertheimer updated the summary of the evidence in 2001 with a quantitative evaluation of randomised trials of counselling, education and other clinical services (Morrison 2001). Together, there was no robust evidence from the UK or North America of the benefits of pharmacists interacting with GPs, aiming to change prescribing with evaluation of clinical or surrogate clinical outcomes.

This thesis aims to describe a pragmatic randomised controlled trial of a new type of educational outreach intervention delivered by pharmacists to GPs and practice nurses. The intervention aims to improve the appropriate prescribing of statins in primary care for patients at highest risk of a clinical event. Both the intervention and trial design are constructed to address shortfalls in the evidence base.

1.10 Potential importance of this work

It remains the case, 20 years after prescribing support and new pharmacy roles were introduced, that there is very little evidence that the new roles adopted by pharmacists can impact significantly on population health in the long term or costs. This lack of empirical evidence may not pose a problem per se, but when decisions need to be made on how best to develop services when a new prescribing drive needs to be implemented, or scale back services in times of austerity, reference to an evidence base for prescribing support becomes important.

In designing and testing an intervention to focus on statins and increase their appropriate use, this study has the potential to inform pharmacy developments in primary care, and improve population health.

Chapter 2 describes the case for focussing on statins in more detail, and uses the lessons from previous research to:

- develop a new prescribing support model;
- design an appropriate trial to test the model.

Chapter 2

Literature review

This literature review includes relevant articles from the published and grey literature until February 2004, at which point the study design was in place and delivery of the SOS intervention had commenced. Learning from literature post 2004 is incorporated into Chapter 6.

The synopsis of the literature review is an appraisal of:

1. Statins and the MRC/BHF Heart Protection Study (HPS) to clarify the strength of evidence for simvastatin 40mg prescribing, and the need for quality and efficiency improvements in statin prescribing in primary care.

2. Educational outreach focussing on prescribing/related topics, designed to change practice, particularly those involving pharmacists. The literature was searched to identify key information and lessons from previous work that would prevent a repeat of any previous work and add to the body of research in the area of Statins, educational outreach, cluster randomised controlled trials and pharmacy.

3. Design features of educational outreach trials because methodological shortfalls are common in previous outreach type trials, our trial methodology needs to be robust.

2.1 Literature review methods

2.1.1 Systematic search of electronic databases

Databases were searched from their inception until February 2004 although the actual date varied depending on the database e.g. for Medline, search period was 1966 to Jan 2004. The following were also searched: British Nursing Index, Pharmline, ERIC, IPA, CINAHL, EBM reviews from Cochrane Register of Controlled Trials, EBM Reviews, NPCRDC, SIGN, NICE, Cochrane Database of Systematic Reviews, EMBASE, National Research Register, PsychINFO and the Effective Healthcare Bulletin.

Selected expert searches (filters) were constructed to increase selectivity and specificity. For the MEDLINE search these included SIGN Medline economics, SIGN Medline systematic reviews and SIGN Medline randomised controlled trial filters. The SIGN EMBASE and CINAHL economic, systematic review and randomised controlled trial filters were applied to the CINAHL and EMBASE database searches respectively. The search strategy used in the MEDLINE search was first run in 2003 then repeated automatically on the first day of each month until October 2011 using an 'Autoalert' function which updated the search on the specified databases on the first day of each subsequent month. Evidence gathered until February 2004 only was incorporated into this literature review.

Search terms

In general, electronic searches were constructed using search terms derived from the following keywords or synonyms: prescribing, drugs, medical education, academic detailing, facilitation, outreach visits, primary care, pharmacists, nurses, general practitioners. If a combination of terms generated a large number of citations, the keyword 'statin' was used. Mapping was used to help find relevant subject headings in databases where 'Map term to subject heading' was available. When this function was not available, the keywords were entered into the keyword fields for that database. All literature searching was limited to human and English language. As an example, the sequence of keywords used in the MEDLINE search is given in Appendix V.

2.1.2 Ad hoc searches

The National Electronic Library of Medicines (www.nelm.nhs.uk/home/default.aspx; part of the National Electronic Library for Health) generated an update twice weekly on current research and opinion relating to medicines, public health, prescribing practice focus and cardiovascular disease.

The British Medical Journal runs an electronic messaging service relating to published research and comment. Through this, the following weekly citations were received and appraised:

- general practice/Family practice/primary care: Health Services Research (http://bmj.com/cgi/collection/health_serv_reasearch?ecoll);
- Non clinical: health economics;

- Statistics and research methods. This highlighted descriptions and examples of randomised controlled trials and systematic reviews.

Bandolier's back catalogue was searched using appropriate keywords (www.jr2.ox.ac.uk/cgi-bin/htsearch).

Hand searches

These included 'The Pharmaceutical Journal' on a weekly and 'Pharmacy in Practice' on a monthly basis.

2.1.3 Selection of relevant articles

Titles and abstracts from search strategies were screened for suitability. Some articles contained new information about statins or new learning on study methodology and were retained on that basis. If a title or abstract was not rejected, the full text was obtained for further evaluation. Bibliographies cited in screened articles were considered and relevant articles appraised as described below.

2.1.4 Critical appraisal of relevant studies

There are known to be difficulties in the funding, design and execution of trials of educational or complex interventions, which may increase the likelihood of there being methodological or analytical weaknesses (Foy 2001; O'Brien 2002). Therefore a systematic, rigorous approach was taken to interpret the scientific papers identified as most relevant to the study. When necessary, one of the following checklists were used:

- for educational interventions, the checklist derived from the Educational Group on Guidelines on Evaluation (Educational Group on Guidelines on Evaluation 1999) and the work by Morrison (Morrison 1999);
- for randomised controlled trials, the checklist adapted from 'Critical Appraisal Skills Programme (CASP)' (Guyatt 1993a and b).

2.1.5 Examples of electronic search outputs

Table 2.1 shows the number of articles generated by a sample of search strategies.

Table 2.1 Summary of outputs from electronic searches

Database	Number of articles
MEDLINE	62 (search #1 see below) 4 (search #2 see below)
Psychinfo	8 (see below)
CINAHL	52
EMBASE	105
Cochrane	1
Pharmline and IPA	18
NRR	7
BNI	7
EBM reviews – Cochrane Central Register of Controlled trials	87
EBM reviews – Cochrane Database of systematic reviews	25
ERIC	0

Figure 1.1 gives the setup and outputs of selected search strategies. Search terms varied according to the database.

Figure 1.1 MEDLINE search #1

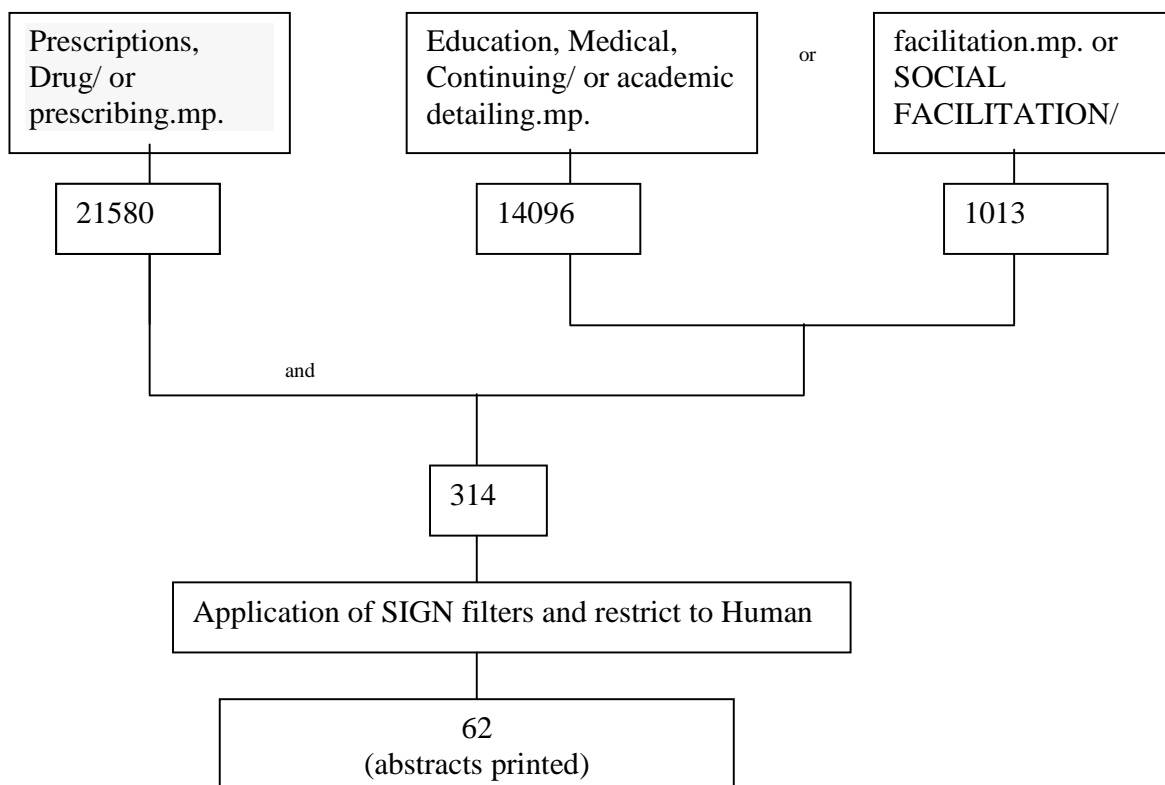


Figure 1.2 MEDLINE search # 2

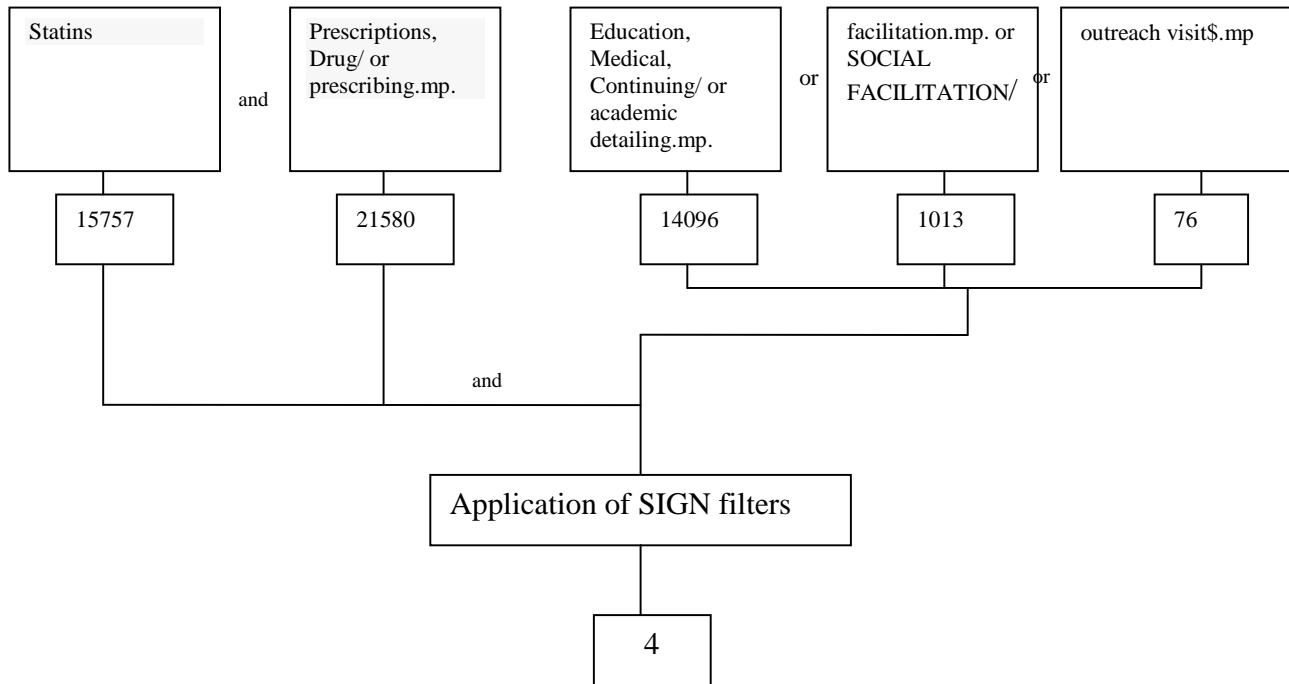
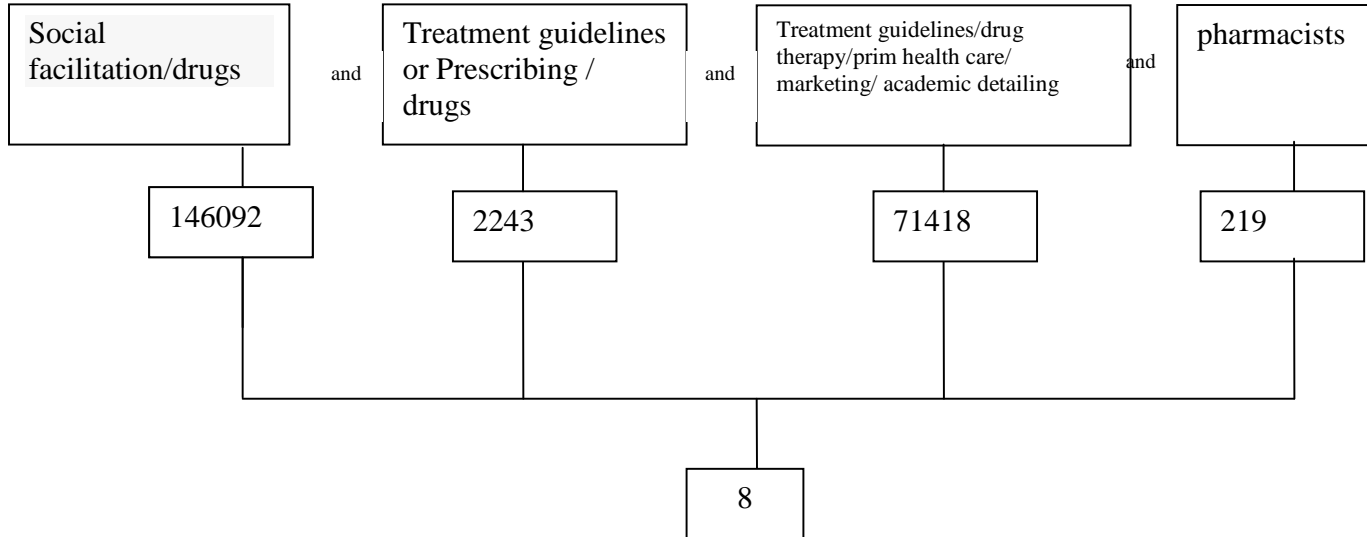


Figure 1.3 PsychINFO search



While many of the manuscripts identified through systematic electronic searches were relevant, other highly relevant papers or reports were identified directly or indirectly through the ad hoc searches described above. All relevant articles from the systematic and ad hoc literature review were then reviewed together. Findings from the most informative articles dated on or before February 2004 are described below.

2.2 Statins

2.2.1 Overview of evidence for effectiveness in secondary prevention

There is an overwhelming body of evidence in favour of prescribing a statin for patients at sufficiently high risk of suffering a vascular event (typically, patients with established cardiovascular disease are considered to be at highest risk) (Scandinavian Simvastatin Survival Study Group 1994; Sacks 1996; LIPID 1998; Shepherd 1995; Downs 1998; Veterans Affairs High Density Lipoprotein Cholesterol Intervention Trial Study Group (VAHIT) 1999; PROSPER study group 2002; Heart Protection Study Collaborative Group 2002). Prior to 2002, the only remaining uncertainty surrounded whether some subgroups of patients, who were not adequately represented in previous trials, should be offered a statin. These included patients with:

- cerebrovascular disease;
- peripheral vascular disease;
- diabetes;
- over 70 years old;
- patients with CHD over 75 years old, within the normal cholesterol range (acknowledging the VAHIT study which showed CHD event risk reduced by a non statin (Veterans Affairs High Density Lipoprotein Cholesterol Intervention Trial Study Group (VAHIT) 1999).

Statins are of proven cost effectiveness when used for secondary prevention (established vascular disease), in diverse patient populations, up to at least 84 years (Ganz 2000; Prosser 2000). From an economic standpoint, therefore, ensuring all patients with vascular disease are offered a statin at a therapeutic dose has the potential to limit the public health impact of vascular disease.

However, inconsistent implementation of research evidence on prescribing (King 2000; Pearson 1997), and adherence to statins (Rasmussen 2007; Benner 2002) requires a change in response from the NHS and patients if the full benefits of statins are to be realised. There may be an additional need to support uptake of the evidence base in practices and patients from areas of socioeconomic disadvantage (a particular problem in Glasgow) who are at greater risk of low adherence (Dani 2007; Davis 2006) and ill health due to vascular disease.

In 2002, the Heart Protection Study Collaborative Group (Heart Protection Study, HPS) identified the benefits of simvastatin 40mg daily for all patients with established vascular disease, regardless of cholesterol level. This study transformed the approach to cholesterol management and guidelines were reconfigured to fit e.g. GG&C Cholesterol guidelines

(Chapter 3, Appendix VIII). These guidelines formed the basis of the educational messages in the Statin Outreach Support (SOS) intervention. Therefore, a more detailed appraisal of the HPS is given below.

2.2.2 Critical appraisal of the HPS

HPS was an independently funded, randomised (allocation concealed), blinded (data collectors, patients, GPs, study nurses, outcome assessors) placebo controlled study with a minimum of 5 years follow up, analysed on an intention to treat basis.

Participants and methods

The number of participants in HPS was greater than all other statin trials combined, with 20,536 patients. Eligible patients were aged 40 - 80 years with CHD, other occlusive vascular disease or diabetes. Research nurses identified eligible patients by screening hospital based records of discharges, relevant outpatient clinics and relevant wards. Therefore all participants had to have a recent history of secondary care admission or attendance at a specialist clinic. By design, this excluded primary care based patients fulfilling the clinical eligibility criteria without previous admission or secondary care attendance. On calculation, 9839 (28.3%) of participants were younger than 65 years, 4891 (23.8%) between 65 and 70 years, 5806 (47.9%) at least 70 years. Twenty four point seven percent of patients (5080) were female. There was no information on numbers of patients aged over 75 years with CHD or over 70 years without CHD; both were of interest because this age of patient had not previously been studied.

A slightly unusual feature of the trial was the exclusion of a significant number of patients who were non adherent with their statin during the 'run-in' period. Over one third (11609/32145 (36.1%)) of those entering the run-in period of the trial did not progress to randomisation. Twenty six percent of those not progressing were described as being non concordant or not keen to enter the trial. This makes generalisability of the study sample more difficult, because one year statin non adherence is estimated to be about 40% for patients with previous cardiovascular events outwith the trial setting, with a greater proportion not taking their statin for primary prevention (Colivicc 2007; Blackburn 2005; Jackevicius 2002; Perreault 2005).

Recruitment criteria in randomised controlled trials often exclude patients with multiple and complex co-morbidities, making it difficult to anticipate efficacy in real world populations in primary care. Unfortunately, in HPS, it was not possible to identify how many patients were diagnosed with more than two disease categories and therefore the applicability of the results to this section of the population remains unanswered. Allocation concealment is assumed on the basis that the list was held at a telephone randomisation centre, as with most other large scale, multicentre studies. Assignment to study group and creation of the allocation sequence were performed separately, minimising this source of bias.

Participating patients and their GPs were blinded to treatment allocation. They were advised of the results from other relevant statin studies, and encouraged to prescribe a non study statin if indicated; therefore 17% of the control group were prescribed a statin. All patients were required to have their cholesterol checked by their own GP during the trial. This design feature

has implications for blinding: participants made aware of their lower cholesterol may have inferred that they were in the active group. The implication is that performance bias was not prevented, and this might have affected other (health seeking) behaviours among the active group participants.

Intervention

Active group participants received simvastatin 40mg daily for 5 years while control group participants received placebo. Timing and duration of the intervention were clearly described. The control group were allowed to take any statin their GP decided to prescribe and analysis accounted for those in the control group who were prescribed a statin by their GP.

The co-prescription of other vascular protective treatments included aspirin, beta blockers, ACE inhibitors, antihypertensives and smoking cessation products. The rates of prescribing of these medicines were shown to be comparable in both groups on entry to the trial. However, no information was available on the relative proportions initiated, stopped, or with dose changes throughout the course of the study, all of which could influence outcomes if not uniformly distributed across active and control groups. Patients were allocated simvastatin or placebo and, unusually, not asked to return for cholesterol or other blood tests. It could be inferred therefore, that patients need not re-attend their practice after starting simvastatin, thus decreasing the need for follow up. However, the heterogeneity of primary care based patients outwith the trial setting may result in a more unpredictable response, necessitating closer follow up.

Outcomes

The choice of primary (all cause vascular and non vascular mortality) and secondary (major coronary events including nonfatal MI or death from CHD, revascularisation, cancer, stroke) endpoints differed from other statin trials by the inclusion of revascularisations. However, baseline history of hospitalisations for revascularisations was not described across intervention and control groups, making it difficult to interpret the true impact of statins on this component of the composite endpoint. The concern here is that statins may have reduced vascularisations more than any other component, with secondary outcomes showing a positive effect for this reason. However, the improvement in the composite primary outcome in the simvastatin group was attributable in roughly equal proportions to the components of death due to coronary and vascular events. The primary outcome was also significantly improved across subgroups including patients with cholesterol less than 5mmol/l. This is an important finding because it legitimises offering simvastatin 40mg to all patients with comparable inclusion criteria, irrespective of starting cholesterol level.

The timing of the appearance of differences in vascular events between groups was consistent with other statin trials. Total and LDL cholesterol decreased in the treatment group during the first year but there was no significant difference in the control group, while there was no divergence in the rates of first major vascular event between groups before one year. For patients taking a statin, two messages arising from these observations are the importance of persisting with the prescription over the long term, and a decrease in cholesterol over the first year is an indication of the statin beginning to reduce the risk of suffering an event thereafter.

The trial profile and accompanying figures show 20,536 patients were accounted for at the end of the study, with a clear description of the reasons why 67 were lost to follow up. All participants were analysed in the groups to which they were randomised.

Table 2.2 All cause mortality in HPS

	Outcome event: All cause mortality		Total
	Yes	No	
Simvastatin Group	1328 (12.9%)	8941(87.1%)	10269
Placebo Group	1507 (14.7%)	8760 (85.3%)	10267

The absolute risk reduction in total mortality was 1.8% (from 14.7 to 12.9%). There was an 18% relative reduction in coronary mortality, absolute rate reduction of 1.2% from 6.9 to 5.7%. The rates of MI, stroke and of revascularisation reduced by approximately 25%.

Communicating evidence from primary research in an understandable, concise way formed an important part of the new intervention planned in the trial. Evidence of benefit (or harm) can be more easily understood if converted into the 'Number Needed to Treat' (NNT). In this case, the NNT to prevent one death was 55, meaning an estimated 55 participants needed to be treated with 40mg simvastatin for 5 years before one patient can benefit. The corollary is that 54 of the 55 patients treated with simvastatin 40mg daily for 5 years do not benefit in this way. From the placebo death rate in the trial, we know that about 15% of patients died over 5 years). NNTs together with 95% Confidence intervals can be calculated from the data presented in the manuscript.

All cause mortality

The proportion of deaths observed in the active and control groups were:
 Simvastatin $1328/10269 = 0.129$ and Placebo $1507/10267 = 0.147$

The Standard Error (SE) = 0.48%; the Absolute Risk Reduction (ARR) is: $14.7\% - 12.9\% = 1.8\%$. The NNT is given by $1/ARR = 55$. Other ways of describing the result are: Relative Risk = 0.88; Odds Ratio = 0.86 and Relative Risk Reduction = 0.12 (12%).

The 95% CI for the ARR is given as $1.8\% \pm 1.96 (0.48) = 0.86\%$ to 2.74% .

The 95% CI for the NNT is reciprocal of this: $100/2.74$ to $100/0.86$ therefore we can be 95% confident that the true population value of the NNT falls within the range 36 – 116, which is wide, reflecting the low absolute number of deaths prevented by simvastatin in this population. The intervention was more effective at preventing major vascular events. In this case, the NNT and associated CI can be calculated as follows:

For any major vascular event (coronary, strokes, revascularisations)

Experimental Event Ratio = 19.8%; Control Event Ratio = 25.2%; RR = 0.79; OR = 0.73; RRR = 0.21; ARR = 5.4%; NNT = 19, CI = 15 – 23. The NNT for revascularisation can be estimated as 39 (29 - 58), and the NNT for a major coronary event as 33 (26 - 46).

Therefore simvastatin 40mg for 5 years decreases all cause mortality (NNT = 55), vascular mortality (NNT = 66), and vascular events (NNT = 33) even in patients with CHD but low cholesterol, or in patients with CVD, PVD or diabetes (if aged over 45 years).

The NNT decreased as the baseline cardiovascular risk increased e.g. 17 patients with a previous MI need to be treated for 5 years with 40mg simvastatin to prevent one patient suffering a vascular event. Key outcomes from HPS are summarised in Table 2.3, in NNT format.

Table 2.3 Number needed to treat estimates from HPS

Outcome	NNT (95% CI)
All cause mortality	55 (36-116)
Any major vascular event	39 (29-58)
Vascular event with diabetes but no CHD	21 (14-42)
Revascularisation	39 (29-58)
Major coronary event	33 (26-46)

Applicability of the results to a primary care population

As an example, for a 75 year old female patient with type 2 diabetes, no CHD, cholesterol controlled, taking an ACE inhibitor and aspirin, the NNT for preventing a vascular event with 5 years of simvastatin 40mg daily is 21 (95% CI: 14 – 42). Therefore we would need to treat 21 patients with comparable characteristics for 5 years, to prevent one patient suffering a vascular event.

Patients enrolled into the trial were those who showed they could take at least 80% of their tablets. This suggests that a comparable primary care cohort would benefit to the same extent if patients were non compliant two days from every ten. This is a useful message to communicate to GPs and patients because good statin adherence is known to be illness driven rather than prevention driven, and some patients need to be reminded they are high risk, even if they are not acutely unwell.

The findings strengthened and extended the results of previous statin trials. Simvastatin 40mg was safe (no need to check cholesterol, LFTs; muscle enzymes only if unexplained muscle symptoms) and the NNTs applied regardless of prior cholesterol, age, previous medical history and concurrent use of other treatments.

Applicability to a pharmacist-led outreach intervention

In primary care, systematic implementation of this evidence requires several complex steps. If agreement is reached on the need and generalisability of the findings to a primary care population then the biggest barrier may be the identification of eligible patients, invitation to attend the practice, re-invitation of those not attending initially, explanation of the reasons for starting a new prescription and provision of a prescription. Thereafter, a system is needed to ensure patients presenting with qualifying diagnoses are managed in the same way. Each step

requires staff commitment and weighing up the opportunity cost. Further, implementing evidence is likely to be more time consuming in areas of deprivation where high risk prevention strategies are notoriously more difficult to implement (ASPIRE Steering Group 1996).

Additional capacity may be required to systematically implement new evidence derived from HPS, because of the current demands on the management of presenting problems at the expense of preventative care (Hutchison 1996). Therefore, it is likely that an educational outreach intervention would help if the pharmacists providing it were also able to identify and create a list of patients eligible for a statin then invite them to appointments in the practice. Providing follow-up for non responders and other 'hard to reach' groups e.g. the housebound, is likely to be welcomed by practices.

2.2.3 The case for improving Statin prescribing

Improving the quality of statin prescribing

From the evidence described above, there is a robust case for prescribing statins for patients with established vascular disease. Prior to HPS, the evidence was less convincing for such a wide spectrum of patients. Publication of HPS led to reappraisal of statin guidelines and together, this is likely to account for the recent increase in statin prescribing, which has surpassed increases in any other risk reducing medicines (Bull 2003; Ramsay 2006). This finding has important implications for the design of a trial testing an intervention to help increase statin prescribing: usual care (due to passive dissemination of guidance) is likely to improve over time and this should be factored into the power calculation. That prescribing increases over time, coinciding with the publication of new evidence, is not a new finding. Calvo and Rubinstein evaluated prescribing pre- and post- publication of successful drug trials. They monitored the incidence of new prescriptions written by physicians in primary care in a 6 month period before and after publication of trials of the following drugs: alendronate, metformin, alpha1-blockers and finasteride. Among their findings was a clear, statistically significant temporal association between prescribing and the publication of the new evidence (Calvo 2002).

However, the literature review gave a convincing account of there being shortfalls in the prescribing and use of lipid lowering agents (ASPIRE steering group 1996; Campbell 1998; Siegel 2000; Ramsay 2006; Sempos 1993; Clinical Quality Improvement Network Investigators 1995; Northridge 1994; McBride 1998; Sueta 1999; McCormick 1999; Aronson 2006; De Wilde 2003; Primatesta 2000; Whincup 2002; De Wilde 2003; Minhas 2004; Smith 2001; Missouriis 2001; Sloan 2001; Frolkis 1998; Hoereger 1998; Reid 2002; Majeed 2000; Fernie 2006; Pearson 2000). Many of these papers reported suboptimal statin prescribing after the publication date of the HPS. The studies varied in design, methodology, sample characteristics, country of origin and severity of cardiovascular disease. There were biases and confounding inherent in most of these due to the absence of a comparator group but the consistent finding was there being considerable scope for improvement in the identification of patients eligible for treatment, statin prescribing in comparison with the evidence base, achievement of target statin doses and achievement of target cholesterol levels.

In EUROASPIRE II, the investigators' found half of those eligible were receiving statins and of those receiving them, half were reaching the target of 5mmol/l (EUROASPIRE II 2001). A

subsequent comparison of EUROASPIRE studies I and II led to the assertion that there was a collective failure across Europe, of practice to achieve the substantial potential among patients with CHD to reduce the risk of recurrent disease and death. Approximately 60% of those patients interviewed across the nine participating countries were prescribed statins between 1999 and 2000 (EUROASPIRE I and II group. 2001). Since then, the introduction of the New General Medical Services (GMS) contract has proved that at least 60% of patients with CVD and diabetes can achieve total cholesterol levels below 5mmol/l (QOF Achievement Data 2005). However, it is not known if there can be any further improvement in uptake beyond the 60% audit target set by the GMS contract, or how many more patients would start and continue to take newly prescribed statins if the health care professionals adopted the best available implementation techniques, informed by implementation research. It is likely that there will remain a significant number of patients who will not take their statin out of choice, even if it were prescribed.

Improving the cost effectiveness of statin prescribing

As there are several statins available, it makes sense to prescribe the least expensive from the options, providing the evidence base for efficacy and adverse effects is similar. Generic simvastatin remains the least expensive statin. It can achieve cholesterol targets in a majority of patients, if prescribed at a 40mg daily dose (Scandinavian Simvastatin Survival Study Group 1994; HPS 2002) and if used instead of more expensive alternatives, could save over £1 billion in 5 years (Aronson 2006).

The Heart Protection Study Collaborative developed a model from the HPS and used it to estimate lifetime risks of vascular events, costs of treatment and hospital admissions in the UK (Heart Protection Study Collaborative 2006). Using the intervention of simvastatin 40mg daily versus placebo for an average of five years, the investigators found that generic simvastatin 40mg for life was cost saving in most age and vascular disease groups studied. Their estimates included patients as young as 35 years and as old as 85 years.

2.2.4 Pharmacist medication review / education for patients with hyperlipidaemia

Several studies (although most were small scale, short follow up, without a control group) described successful pharmacist-led medication review, provided directly to patients with hyperlipidaemia, aiming to lower blood cholesterol levels (Simpson 2004; Peterson 2004; Ellis 2000, Tsuyuki 2004; Bozovich 2000; Cording 2002; Traywick 2003).

Alternatively, and possibly more efficiently, pharmacists could target GPs rather than patients in an attempt to provide a greater impact on a larger number of patients, and to maintain change for longer than can be achieved with the individual patient consultation route of face to face medication review. Educational outreach offers an untested way of achieving this aim, if coupled with organisational support at general practice level. Evidence of the existence, feasibility and effectiveness of such a multifaceted approach is lacking.

2.3 Educational Outreach: features of the intervention

2.3.1 Overview

Educational Outreach can change health professionals' prescribing behaviour (New 2004; Boardman 1999; De Wilde 2003; Davis 2003). It involves a face to face meeting between a person knowledgeable in therapeutics and a healthcare professional, in the healthcare professional's own setting. It commonly incorporates the provision of feedback on prescribing issues and the following key features and techniques are thought to maximise the chances of educational messages being understood and the learning being implemented:

- Focussing on a targeted, small group of clinicians;
- Defining clear educational and behavioural objectives;
- Establishing credibility;
- Stimulating active participation;
- Using concise graphic educational material;
- Highlighting and repeating essential messages;
- Providing positive reinforcement in follow up visits.

(Avorn 1983; van Eijk 2001; Soumerai 1990; Thomson 2002).

The term 'Detailing' was originally coined to describe a form of educational outreach pioneered by the Pharmaceutical Industry through representatives promoting their products. Marketing and selling strategies are incorporated, tailored to the doctor's personality, practice style and preferences. Acknowledging the usefulness of this approach in a commercial, for-profit sense, the methods have been applied to benefit the 'not for profit' sectors e.g. the National Health Service. This led to the terms 'Public interest' or 'academic' detailing, and the process of non commercial, short, face to face, in-service interactive education by a trusted outsider trying to promote evidence based choices among physicians. The median improvement in prescribing from this approach is estimated to be approximately 6% with a range from -4% to 17%, up to 1 year (Grimshaw 2004) although Avorn achieved a difference of 18% (Avorn 1983: see Table 2.4). Core features of this complex model are not well understood. There is no consensus or guidance on how narrow or wide the topic should be, or the relative efficacy of components e.g. written compared with face to face feedback. Frequency of contacts between pharmacist and prescriber vary between studies. Some suggest that eight, one hour sessions per practice are sufficient to effect prescribing change at practice level (Squires 1997), while others recommend meetings every 4 – 8 weeks, of one hour duration (Pilling 1998), but there is no consensus, partly because of the differences in context, content and delivery, topics, training of staff involved.

Limitations of current models

Compared with conventional group based educational meetings, detailing is thought to be more effective (Bernal-Delgado 2002; Thomson 2002). Educational meetings generally focus on a wider subject, take place outwith the provider's practice and involve groups of professionals together. To date, the published reports of educational outreach describe

interventions focussing on educational exchange, without any practical, ‘hands on’ assistance to introduce changes to practice, or without much thought about how changed practice can be sustained (O’Brien 2002). The messages conveyed during educational meetings are not usually individualised to each GP’s needs, unlike the approach taken by pharmaceutical industry representatives, who make every attempt to tailor their messages to meet GPs’ real or perceived needs. Marketing and behavioural or personality profiling are used to achieve this end.

The level of interactivity in studies of detailing is difficult to ascertain from available evidence. Delivery of outreach appears to involve prioritisation of the message (usually abbreviated clinical guidance) over the process by which the message is communicated. This runs the risk of failing to acknowledge the GP’s circumstances, baseline prescribing habits, beliefs, opinions and not least, patient preferences. In 2000, the Medical Research Council acknowledged the importance of basing implementation on a scientific understanding of the behaviours that may need to change, the relevant decision making processes and the barriers and facilitators of change (Medical Research Council 2000). In view of this guidance, and the increasing reliance on prescribing as a means of tackling or preventing ill health, it is timely to introduce a new form of detailing, which supports implementation by tailoring the messages to each GP, and providing practical help in addition to educational outreach.

2.3.2 Theoretical principles

Theory building and testing are important considerations for developing new approaches to prescribing improvement. In 1990, Raisch produced a useful model of methods to influence prescribing (Raisch 1990a, 1990b). He drew on four bodies of literature to develop his theoretical model and suggested that the greatest chance of success comes from constructing an intervention which incorporates:

- Theoretical prescribing models;
- Theories of persuasion;
- Research articles of programmes to improve prescribing;
- Theories of human inference.

The prescribing habits of individuals were acknowledged to be relatively stable over time. Changes usually occur slowly and as a result of various influences including scientific papers, specialist recommendations, postgraduate educational or practice meetings, feedback from patients and the pharmaceutical industry. Lack of knowledge is only one reason for suboptimal prescribing and may not be the factor limiting change in many cases. Raisch also suggested that of the numerous factors influencing prescribing decisions, it is likely that some are rational and others irrational. Accepting this to be true, and assuming the general aim is to change prescribing decisions in line with standards set out in clinical / prescribing guidelines, it follows that rational influences are more easily identified and resolved than irrational influences. Depending on the relative weight of rational and irrational influences, this is a limitation to any prescribing support model and should be borne in mind. Ignorance, incompetence, poor management, and sometimes a deliberate disregard of established knowledge may get in the way of best practice when it comes to implementation of guidelines in general (Clinical Resource and Audit Group 1993). This approach may also be seen as displaying healthy scepticism because guidelines are not always based on impartial, best

evidence (Delamothe 1999; Grol 1997). Not all patients fit a guideline algorithm for each of their conditions. Doctors may be exercising a conservative approach to minimising the risk of exposing patients to treatments that (in some cases) have not yet gained sufficient exposure in a real world population. Practitioners may regard guidelines as documents that focus on scientific knowledge rather than the needs of their end users (Fairhurst 1998). There are many examples in general practice of so called “clinical evidence” being of questionable quality, relevance, objectivity or simply out of date by the time it arrives in practices. As one GP put it: “the fickleness of evidence is inconvenient but would be easier to live with if it was more widely acknowledged in discussions of implementation” (Temple 2002).

From the available evidence, a novel intervention should include features which enable identification or anticipation of individual GPs’ reasons for not implementing the evidence.

If a guideline has features that are conducive to increasing uptake, this is likely to improve implementation potential. Several features are known to be useful, including congruence with existing prescribing norms, precise descriptions of actions required and the need for the message to be compatible with GPs’ values (Grol 1997; Grol 1998; Burgers 2003). Involvement of GPs in the process of guideline development may be consistently effective as a means of improving prescribing (Pearson 2003).

Information transfer

Theories of information transfer are relevant to prescribing change interventions because few facts are learned unless they are presented in ways that enhance retention. It is therefore important to link new prescribing information to what the prescriber already knows. This creates the need to find out what the prescriber knows in advance – a marketing technique used extensively by the pharmaceutical industry. If prescribing information is presented in context e.g. at the time of an eligible patient’s appointment, timely retrieval is more likely. Active discussion e.g. using therapeutic dilemmas or clinical scenarios from practice may also help ensure detailing messages are absorbed, retained and used in practice.

There is a recognised gulf between what is known about changing prescribing behaviour and what is practised by those aiming to change it. This has led to a range of theories describing how to improve dissemination and implementation. These can be applied at the individual or health care system level (Smith 2000; Prochaska 1984; Bero 1998).

Some theories are intuitive e.g. Fraser argued that as evidence is translated into practice by the pushing out of ideas by the spreaders of best evidence, change was more likely to take place if the focus is on the prescriber (who they describe as the ‘adopter’) (Fraser 2003). It stands to reason that adult learning and persuasive communication theories could be put to good use in the move to improve prescribing. If the theories are applied by the person instigating the change in prescribing (in this case, the pharmacist), they suggest the importance of using repetition and reinforcement, recommending alternative prescribing strategies, supporting recommendations by credible third parties e.g. expert clinicians. Offering evidence based, unbiased advice and stimulating interactive discussion are ways of establishing and sustaining engagement compared to other strategies e.g. passive dissemination of sponsored promotional material. Other features likely to increase the ability to improve information transfer and the

uptake of better prescribing include features relating to the pharmacist delivering the information e.g. credibility, expertise in the relevant topic area (Lipton 1995).

In reviewing the literature and combining this learning with observations from working in general practices in the past 15 years, it appears that prescribing problems cannot all be solved through ready access to evidence based medicine. Freeman demonstrated this point by showing that evidence based medicine can be viewed as a language to describe formalised explicit knowledge (Freeman 2001). In contrast, tacit knowledge includes intuition and problem solving ability that is gained through experience and interaction with people. It is important in decision making and is not often made explicit or externalised. In constructing a new educational outreach-type model, it is important to create an environment for the opportunities to arise when pharmacist-detailers find out GPs' tacit knowledge about the detailing topic. One way to do this could be to arrange a face to face meeting to explore tacit knowledge. Another way to find this out is to carefully gather information from past prescribing decisions.

Patient perspectives

A frequently overlooked consideration in prescribing change models is the importance of patients' beliefs and choices. Patient related barriers e.g. their beliefs and preferences ought to be acknowledged and addressed (Lipton 1995). In reviewing educational interventions targeted directly at patients, Mullen identified several principles which, if addressed, rendered the approach more effective (Mullen 1985). While Mullen's principles do not apply directly to the model of pharmacists detailing with GPs, they are congruent with many of the techniques used as part of the academic detailing approach. These include provision of advice that is relevant to the receiver's circumstances, involvement of the receiver in the design of the intervention, reinforcing desirable changed behaviours, anticipating and addressing practical barriers to changing behaviour and the importance of delivering educational messages through multiple media e.g. written and verbal. A scoring system based on these principles has since been used to evaluate the quality of inter-professional educational interventions, confirming the potential suitability of Mullen's work in this context (Cooper 2001).

2.3.3 Underpinning intervention design with theoretical approaches

It is recommended that the design of interventions aiming to change health care professionals' practice is underpinned by theoretical principles of behavioural change including adult learning theory (Foy 2001; Medical Research Council 2000, 2011). An understanding of theories of behavioural change and acknowledgement of factors known to influence prescribing practice is therefore a useful starting point to designing a novel intervention to change prescribing (Foy 2001). As with complex interventions in general, this is better understood in the context of other relevant intervening variables. Literature in this area is diverse and it is often difficult to extract practical lessons that could be transferred into a new prescribing change model. However a useful, pragmatic description of a range of factors recognised (by doctors) as important in changing clinical practice is given by Allery (1997). Fifty GPs and 50 consultants were interviewed and using a critical incident technique, they ascertained categories of reasons influencing their clinical practice. While the scientific

validity of their findings was not helped by the absence of a comparator group, (they did not ask a comparable group of GPs who did not make changes), it was clear that help with organisational factors combined with education, and contact with an independent professional e.g. a pharmacist, was regarded as a positive influence. They recommended that a wide range of factors need to be considered in the provision and evaluation of educational activities, because of the wide range of factors involved in changing practice.

Schwartz explored 114 doctors' motivations for apparently inappropriate prescribing decisions within a larger randomised controlled trial (Schwartz 1989). Of the 110 responses elicited, the most common reason for prescribing medicines known to be of limited usefulness was patient demand. Most prescribing decisions seek to balance perceived efficacy with perceived risk of adverse effects. The authors recommended that greater attention should be paid to attitudes and motivations concerning suboptimal prescribing if 'detailing' programmes are to be successful. This observation has implications for the design of a study testing a novel outreach model: targeting prescribers known to prescribe sub-optimally (in comparison with clinical guidelines) is more likely to generate positive results compared with an untargeted approach. However, in the National Health Service, the level of equity is important, and in primary care general practices, all patients who are eligible for a statin or eligible for an optimal dose (i.e. those not prescribed a statin or those prescribed one, but at a dose less than guideline recommendations) ought to be offered one. These patients exist in every practice therefore targeting of all practices may be necessary.

In 1996, Armstrong interviewed a purposeful sample of 18 GPs from London and hypothesised that there were three models of prescribing change (Armstrong 1996). Notes taken during semi-structured interviews were analysed and identified a challenge model, a continuity model and an accumulation model. An important practical conclusion from this work was the unanimous view of the participating GPs that the initial change in prescribing was precarious and needed reinforcement. This finding coincides with much of the literature describing effective educational outreach programmes, where repeated visits serve the purpose of reinforcing desired change (Oxman 1995). A similar observation was noted from effective programmes of changing patients' health behaviours including adherence to medicines (Dolan Mullen 1985). Reinforcement and support for the initial steps towards prescribing change therefore appear worth integrating into a novel educational outreach model. Cognisance should also be given to doctors' overriding concern when considering whether to prescribe: preservation of the doctor-patient relationship. Non clinical factors have an important influence on prescribing e.g. attitudes, perceptions and experiences of the GP (Bradley 1992). All of these factors should be acknowledged before introducing an educational programme.

Prescribing support interventions should be designed in a way that enables the providers to recognise the barriers known to limit the translation of evidence into practice. Different adopters are likely to present different (often personal and wholly legitimate) reasons for not following the evidence based model of prescribing (Veldhuis 1998; McColl 1998; Freeman 2001; Sweeney 1998). Organisational barriers are a recurrent theme. The EBOR study investigators were unsuccessful in their attempt to change clinical practice following outreach visits, citing organisational difficulties as one of the main barriers to implementation (Freemantle 1999). Different barriers are likely to arise in different practices, and between individuals in the same practice, so a commonsense approach would suggest separate strategies are needed to overcome these. In Glasgow, we have found that different approaches are needed to engage different patient subgroups. For example, inviting Urdu or Punjabi speaking South Asians in their native language through a phone call is more successful than

using English. We have found that a pro-active, empathic approach, tailoring appointments to the individual's availability is more likely to lead to attendance in patient groups usually perceived as 'hard to reach' in areas of socioeconomic deprivation (Lowrie 2010b internal report). Communicating using methods used routinely by the individual e.g. appropriate language or texting on a mobile phone, is more likely to bring about success than a printed letter, particularly if levels of literacy are low (O'Donnell 2009 internal report; Fisk 2006). In their critical review of studies of educational programmes designed to improve prescribing in North America, Figueiras concluded that the more personalised the intervention to the prescribers' needs, the more effective the strategy is likely to be (Figueiras 2001). The authors substantiated this by conducting their own pragmatic controlled trial evaluating the effectiveness of two multifaceted educational strategies aimed at improving prescribing standards in primary care. Comparing one to one education with group sessions, focussing on reduced prescribing of non-steroidal anti-inflammatory drugs, they showed that single outreach visits of one to one sessions were more effective than group sessions.

In 2004, Schumock asked a sample of 150 doctors, pharmacists and formulary committee members to express their opinions as to the importance of factors influencing prescribing decisions. They found significant differences between professional groups. Doctors rated the recommendations of pharmacists, formulary committee members, prescribing guidelines and cost comparisons of lower influence than the pharmacists themselves (Schumock 2004). If generalisable, this result highlights the importance of asking prescribers to identify their biggest prescribing influences, and seeking the views of whoever the prescriber identifies as being educationally influential.

GPs' perspectives of the utility of detailing information are sparse, but McColl produced a useful précis. He asked a sample of 302 GPs from Wessex, UK, what they rated most highly as helping clinical decision making. Using a semi structured questionnaire, they reported that GPs wanted evidence presented in short, understandable packets, with recognisable quality standards, using understandable descriptions e.g. NNTs of useful outcomes (McColl 1998). None of their requirements are too challenging, even in the current resource restricted NHS environment.

2.3.4 Tailoring interventions to overcome implementation barriers

From Grol's summary of factors limiting or restricting behavioural change, it is possible to identify barriers which may need to be overcome before implementing clinical guidelines:

- Orientation: becoming informed about the existence of new guidelines; feeling interest and commitment;
- Insight: understanding the guidelines, awareness of gaps in own performance and the need to change;
- Acceptance: positive attitude to the new guidelines accompanied by intention to change;
- Change: implementation in practice, experimentation, recognition of positive outcomes and maintenance of change (Grol 1992).

Differences between guideline recommendations and prescribing in practice are inevitable when guidelines are drawn from discrete studies in populations and settings that may be far

removed from usual care. Many other factors contribute e.g. the organisational context of the practice or the nature of the clinical or prescribing topic compared with the priority assigned to it in the practices under scrutiny. It is therefore unreasonable to aspire to 100% guideline adherence in any given topic and it seems likely that tailoring interventions to address these issues in a GP by GP and Practice by Practice basis will have most chance of overcoming implementation barriers. Bero concurred with this view, suggesting that the methods of implementing evidence based prescribing should be guided by evidence on their effectiveness, the nature of the change being suggested and a prior assessment of the obstacles to change (Bero 1998).

Fretheim constructed a tailored intervention incorporating an educational outreach visit with audit and feedback and computerised practice based reminders (Fretheim 2003). Pop up reminders appeared on physicians' computer system in response to a consultation with a patient who had high blood pressure or high cholesterol. This enabled rapid calculation of cardiovascular risk and printed educational material for the patient; both factors had been previously identified as rate limiting.

Psychological methods have been used to guide GPs in the implementation of guidelines for depression in primary care (Baker 2001). Baker used content analysis of interviews with GPs about their performance. This enabled assessment of the likely obstacles to guideline-led depression management and pinpointed a psychological theory that best explained the relevant obstacle. Implementation methods were constructed in response to these theories and obstacles, and GPs were encouraged to adopt the recommended implementation methods. Important learning from this trial included the importance of the individualised discussion with each GP as a means of identifying reasons why the guideline evidence was not implemented, followed by tailoring of interventions to support the GP to adopt evidence based practice. The researchers did not seek to identify organisational or other obstacles at the practice level because it was not possible to change them.

In some cases, organisational inertia may be the rate limiting step and needs to be considered then tackled. For example, a new trial investigating statin prescribing for a cohort previously untreated would first require identification of those eligible to receive it within each practice. Following this, an invitation to attend an appointment, and offer of a statin would be required. Each step takes time and a systematic approach; adequate and persistent call and recall underpinned by accurate and complete practice based disease registers to maximise uptake and minimise dropout, particularly in areas where health literacy is poor and engagement with preventative or screening appointments is low.

Fretheim attempted to implement an educational intervention aiming to improve prescribing of antihypertensive and cholesterol lowering medicines. In their analysis, they used structured reflection and focus groups to identify barriers to uptake of their educational messages (Fretheim 2004). Their findings were comparable to that of other teams: gaining commitment to change is predictive of actual change, which is a useful approach, easily replicated (Wakefield 2003), and worthwhile incorporating into a novel detailing approach.

In the international Drug Education Project, a new educational programme facilitated by GPs or pharmacists for peer groups of doctors to improve the treatment of asthma patients in the Netherlands, Norway, Slovakia and Sweden, was developed and tested (Veninga 1999). The multicentre trial design was parallel, randomised and controlled to test the effect of an educational programme on competence and prescribing. The intervention comprised

individualised feedback on the underlying reasons for prescribing choices. Feedback was presented and discussed in small peer groups. Significant improvements were noted in all competence and prescribing outcomes in all countries except for Sweden, where improvements were made on all outcomes but the effect failed to reach statistical significance. Control group practices received prescribing guidelines only. The authors comment that the tailored approach was the key to effecting change. This result is striking because of the consistently positive effect despite the between, and within, country variation in continuing medical education programmes, organisational barriers to change, different baseline prescribing behaviours and attitudes of GPs. In reviewing this paper, it becomes apparent that a tailored intervention (if carried out effectively) may be more likely to work across different healthcare settings because it identifies and seeks to address the expressed educational and organisational needs of each individual, whatever the individual's experience, background or practice organisation.

Another group of researchers tailored their outreach visits to the needs of each practice and found that this feature predicted effectiveness (Hulscher 1998). However, the extent to which they enabled the doctor to shape the educational exchange led to wide variation in the intensity and duration of their input. In their discussion, they called for standardisation of visits and standardisation of the skill-set of those delivering them, from an economic perspective.

Prescribing or other healthcare professional change interventions should be designed in a way that enables detection of the barriers known to limit the translation of evidence into practice. It is likely that these interventions need to be tailored to meet the needs of individual prescribers because of the considerable variation in the reasons given for not following the evidence based model of prescribing (Veldhuis 1998; McColl 1998; Freeman 2001; Sweeney 1998). Tailoring of prescribing support in line with each individual GP's preferred learning method is an approach backed up by adult learning theory, and common sense. In their critical review of studies of educational programmes designed to improve prescribing in North America, Figueiras concluded that interventions personalised to the prescribers' needs are more likely to be effective (Figueiras 2001). From a more pragmatic standpoint, the onus is on the person delivering the educational support, to tailor it in advance. This should happen, out of courtesy and acknowledging that GPs, like other front-line healthcare professionals in the NHS, are busy people with little time to waste on unnecessary or inefficient learning exercises. For educational interventions focussing on updating pre-existing knowledge, aiming to improve prescribing practice, it is likely that support should include constructing and updating lists of patients eligible for prescribing change, generating letters of invitation to eligible patients, ensuring call and recall systems are updated and applied, rather than reiterating guidelines.

Most GPs do not work independently. Instead, they work as part of a practice team and therefore, educational interventions aiming to change prescribing need to be seen in the practice context. There will be organisational barriers and difficulties at practice level that need to be identified and overcome. For example, implementation of the evidence base around offering statins to all patients with established vascular disease will require careful verification of patients most likely to benefit. In addition, it cannot be assumed that acquisition of knowledge about the 'best' treatment strategy is sufficient to overcome change: the rate limiting steps may be the systematic call and recall, chasing of non attendees, not to mention the need to overcome prescribing inertia (Nazareth 2002).

Anticipation of barriers to implementing change appears to be the exception rather than the rule, in previous research. In keeping with the majority of educational outreach trials, Doyne constructed educational modules without involving the end users. They did not seek to

discover barriers to implementation in their randomised controlled trial involving an intervention to change antibiotic prescribing for acute conditions. Their control group received summary information by post only. Their intervention characteristics were poorly described; it is likely that they presented information in a didactic fashion, in small groups, without much discussion or interaction. Their ‘academic detailing’ model failed to achieve a statistically significant effect when the impact was measured by the under, or over, use of amoxicillin or cephalosporin antibiotics respectively (Doynes 2004).

The EBOR trialists were unsuccessful in their attempt to change clinical practice following tailored outreach visits. In their discussion, they cite organisational difficulties as one of the main barriers to implementation, rather than a mismatch between the intervention and the GPs’ information needs (Nazareth 2002). In particular, they lamented that they did not anticipate the level of organisational difficulties they encountered e.g. setting up a disease register and the call/recall problems in practices.

The Cochrane database of systematic reviews assessed studies of tailored interventions to overcome identified barriers to health professionals’ performance (Shaw 2005). Inclusion criteria were typically selective: randomised controlled trials that reported objectively measured professional practice in which at least one group received an intervention designed to address prospectively identified barriers to change. While one analysis of their findings found tailored interventions to be more effective (Odds Ratio 2.18 (95% CI 1.09 – 4.34; $p = 0.026$), another analysis using a different criteria gave a comparable odds ratio, but failed to reach statistical significance. Overall, they concluded there was insufficient evidence to confirm interventions tailored prospectively to identify barriers actually improve care and patient outcomes. However, in defence of some of the available evidence, stringent criteria were applied before accepting studies into the review. While this approach confirms the rigour of the studies included, it leads to many useful studies being rejected, and raises the question of publication bias in choosing only published trials. In addition, sufficient funding and time are not always available to deliver and evaluate complex interventions in primary care. Further, complex interventions have, by definition, several interacting components, making it difficult to pinpoint the key feature.

For general practice level interventions in the United Kingdom, it appears that involving participant GPs in the design of their own intervention could be important (Langham 2002).

2.3.5 Features of academic detailing or educational outreach for prescribing

In the original report of academic detailing, Soumerai described a comprehensive list of features of the intervention (Soumerai 1987). Brevity, repetition and reinforcement of desired prescribing practices were cited as key factors contributing to the success of their educational messages (Soumerai 1990). The same authors had previously concluded, from a randomised controlled trial involving 435 doctors, that face to face educational sessions are effective in improving prescribing practices. Their sample of doctors included different age groups, speciality, urban/rural setting or extent of prior prescribing of the target drug groups.

In another report evaluating the effectiveness of academic detailing as a means of improving aspects of health professionals’ practices (focusing on mental health care), Soumerai stressed the importance of person to person contact with credible experts and the provision of

information for GPs to try structured alternatives to help facilitate change. Four trials which had tested detailing as a means of improving mental health care were reviewed. Detailing was found to be effective as a means of reducing the overuse of unnecessary medicines, however, improvements in markers of mental health or the detection of mental health problems remained unchanged (Soumerai 1998).

Since then, many different permutations of the detailing model have been delivered and tested. The following appear to be important, and will be carried forward into the new model described and tested in the thesis.

2.3.5.1 Multifaceted approaches

Multifaceted interventions have tended to anticipate, facilitate and reinforce desired behaviours. They appear more likely to succeed compared with single strategies or single interventions (*Getting evidence into practice* 1998; Wensing 1998; Grol 1992). It follows that approaches to changing prescribing that use a greater number of evidence based strands may be more effective than those using less. Madridejos-Mora used a combination of educational recommendations and feedback of individualised prescribing, to improve prescribing quality (Madridejos-Mora 2004). Quality in this context was defined as improvements in the uptake of evidence based recommendations for prescribing of non-steroidal anti-inflammatories, ulcer healing drugs and antibiotics. Improvements in the quality of prescribing, particularly reducing overprescribing, was noted in practices exposed to their combination approach compared with a single approach. However, their description of the intervention is short on detail, limiting further critical appraisal.

Few trials other than that conducted by Madridejos-Mora have attempted to combine and compare more than two different components. None have accessed practice held patient level information and used that to identify patients who are eligible for change, then supported GPs to contact all eligible patients systematically.

Attempting to influence patient behaviour is rare; only one account of academic detailing reported the use of posters in waiting areas together with patient level education. When the dual approach of GP education and patient information were combined, the intervention proved successful and the authors cited the combination as one of the key reasons for effectiveness (Harris 2003).

While multifaceted approaches may be more likely to generate positive outcomes, simple approaches should not be overlooked because they may be easier, quicker and cheaper to deliver and evaluate. For example, Hux conducted a randomised controlled trial of antibiotic education and confidential feedback to GPs in Canada. They hypothesised that a decrease in the prescribing of inappropriate antibiotics and an increase in first line antibiotics would result. In achieving their primary outcome, they concluded that the simplicity of their programme, particularly the confidential aspect of their feedback, was vital in achieving desired outcomes (Hux 1999).

2.3.5.2 Multiple therapeutic topics

Some researchers, like Madridejos-Mora, tried to effect change in several therapeutic areas within the same educational outreach programme. Assuming the detailing approach is effective, it might appear more efficient to deliver multiple messages. However, this approach needs to be balanced against the inevitable dilution of message when several are communicated at the same time. An associated reduction in effect size may be expected; a greater magnitude of effect might be achievable if only one focussed topic was chosen.

In their detailing intervention to encourage GPs to avoid the many pitfalls from polypharmacy for the community dwelling elderly, Allard communicated multiple educational messages in the hope of changing physicians' prescribing patterns accordingly (Allard 2001). Using a primary outcome of 'potentially inappropriate prescriptions', it was perhaps not surprising that there were no statistically significant improvement in the intervention group because of the number of interventions recommended and the complexity of the steps involved in translating this information into practice. In a similar approach, the EBOR trialists tried to demonstrate a difference through their intervention, focussing their educational messages on multiple drug based topics. They failed to detect any difference in prescribing overall but had some measure of success in smaller practices compared with larger practices (Nazareth 2002).

Crotty aimed to reduce falls and stroke risk in the elderly, through the delivery of two (pharmacist-led) educational outreach visits to nursing and medical staff in residential care homes (Crotty 2004). The study design was a randomised controlled trial, set in Australia. As risk factors for falls and stroke are multifactorial, the investigators covered multiple topics during their two detailing visits. Outcomes included a reduction in the percentage of falls, increase in the prescribing of aspirin, and reductions in the prescribing of various psychotropic medicines. In explaining the lack of achievement of any of these outcomes, the authors cite the difficulties they found in identifying and influencing the multiple contributors (and therefore barriers to change) of care for patients in the residential care setting. These included the need to explore barriers posed by physicians, nurses, care staff and family. If Crotty had carefully considered the suggested reasons for the success of earlier detailing interventions delivered in residential care settings e.g. Avorn 1983, they might have noted the importance of anticipating barriers created by different care pathways and healthcare professionals' or carers' views within care homes. This may have prompted tailoring of their intervention accordingly.

Avorn and Soumerai believed there to be a need to meet with all stakeholders in order to be in a position to identify and overcome barriers to implementation of their educational messages. Similarly, researchers in Sweden held bi-monthly outreach meetings with all caregivers in nursing homes recruited in a randomised controlled trial, over a 12 month period. The aim was to test the impact of their detailing package of multiple therapeutic topics, on the quality and quantity of psychotropic drug prescribing. (Schmidt 1998). They managed to achieve their desired effect. They suggested that improved teamwork in the nursing homes allocated to the experimental group was a key factor. It could be that repeated contacts with staff over 12 months gave ample opportunity to reinforce the key messages, deliver feedback on improved performance and enabled stronger working relationships to develop, all of which are consistent with learning from theoretical approaches of behaviour change. Two important differences between the study designs of Crotty's trial and that of the Swedish team were the degree of anticipation of the barriers to change and the length/intensity of the intervention. It

stands to reason that anticipating barriers to change and delivering a more intense intervention will increase the chances of a successful outcome.

Goldberg conducted a randomised controlled trial comparing the effect of continuous quality improvement teams with academic detailing (Goldberg 1998). They focussed on several broad topics: hypertension prescribing, blood pressure control, depression recognition, prescribing of older tricyclic antidepressants and scoring of patients' depression ratings using a novel depression scale. Process measures (prescribing, symptom scores) and blood pressure readings were collected. Academic detailing achieved a slightly greater effect size than the continuous quality improvement teams but neither improvement reached statistical significance. The authors concluded that academic detailing and continuous quality improvement were ineffective in improving hypertension and depression guideline compliance. Alternatively, their results may be highly conditional: the choice of multiple topics was overambitious a priori (certainly a posteriori), and a lack of anticipation of multiple barriers may have obscured the effect of the intervention.

As there are many interacting features to the complex interventions delivered in the context of the trials described above, the features cannot be viewed in isolation. However, the trend appears to favour effectiveness when fewer topics are covered. Any reduced effectiveness of the intervention as a result of covering multiple topics could be attenuated or overcome by anticipation of barriers to change and addressing these, and adhering to the detailing principles and behavioural change techniques described in the original work (Avorn 1983).

It is also worth noting that the choice of therapeutic topic is likely to have a bearing on outcomes in this type of comparative effectiveness research. From information generated by the literature search and associated reading, it appears that most published outreach trials have focussed on changing antibiotic prescribing for acute conditions, over the short term. These trials have been conducted in Australia, North America, Canada or the Netherlands (De Santis 1994; Schaffner 1983; Ilett 2000; Welschen 2004; Gonzales 1999; Zwar 1999). This choice of therapeutic topic provides frequent consultations and ample opportunity to use new approaches to prescribing, but possibly limits the ability to evaluate the impact on longer term effects or on LTC management.

2.3.5.3 Number of visits

Most trials involve a single visit to general practices or primary care centres by the detailer. While single visits might be expected to achieve statistically significant changes in short term, frequently prescribed items, uncertainty surrounds whether the changes persist. All else being equal, it follows that multiple visits are more likely to achieve longer lasting changes. In a study by Peterson, a pharmacist visited GPs once only, after sending educational material in advance, but the duration of the effect was not evaluated beyond the end of the short intervention period (Peterson 1996).

When sufficient information on the number of visits is available, fewer visits tend to predict less chance of success. Witt delivered a single visit to encourage the uptake of an asthma guideline in general practice (Witt 2004). Using changes in sales of asthma medicines as the outcome measure, their approach failed to make an impact. While the authors discuss a few reasons for the poor uptake, their expectation was that GPs would improve adherence to a

complex guideline and sustain improvements, after only one visit from an academic detailer. There was no reference to a pilot study and the sample size calculation was not described in sufficient detail to enable further appraisal of this work.

The apparent increased likelihood of effectiveness following multiple visits may need to be balanced with acceptability and cost of repeated outreach visits. Gask found that two face to face visits per year by a detailer to general practices was feasible and acceptable to GPs in Belgium (Gask 2004). Crotty found that residential care home physicians accepted two outreach visits (Crotty 2004). In delivering their successful educational package to GPs in Anglia, Fender met with practices on 2 separate occasions (Fender 1999). Yeo and colleagues in Australian general practice describe a controlled trial involving three visits aiming to reduce prescribing of benzodiazepines and related medicines (Yeo 1994). While they do not report any change in prescribing behavior, the GPs who received the face to face support rated their benzodiazepine prescribing as much improved but objective assessment of their prescribing did not show any change. In their discussion, the authors reflected on the components of their intervention and stressed the importance of the initial meeting to “establish rapport”. Overall, they interpreted their findings as a reminder that “we do not always do what we mean to do, and we do not always do what we think we do”. Missing in their approach was anticipation of practical barriers to changing prescribing. For example, the detailers failed to identify those patients who were eligible for benzodiazepine reduction or discontinuation, or provide the GPs with this information to facilitate change.

Soumerai appears to be the only researcher to have speculated on the dose-response of increasing the number of outreach visits. He conducted a randomised controlled trial of the effectiveness of face to face visits by clinical pharmacists, involving 435 doctors. They observed an approximate doubling of the magnitude of change in their targeted medicines when the number of visits was increased from one to two (Soumerai 1987).

In a randomised controlled trial of practice based education (using principles of academic detailing) in east London by Feder, guidelines for asthma and diabetes were actively disseminated. Focusing on practice based small group multidisciplinary educational outreach sessions, the authors visited practices on three occasions. While the duration of meetings and the interval between meetings was not reported, the effects were positive and the three visits were viewed as an integral part of the successful model (Feder 1995). The investigators appear to have adhered to the principles of academic detailing during their meetings with practices. They also encouraged practices to make improvements in the accuracy of their disease registers.

Only one report from the literature review described GP preferences regarding the frequency of academic detailing visits in practices. A feasibility study based in Belgium invited 184 physicians to receive two visits from an academic detailer focusing on Non Steroidal Anti Inflammatory painkillers. One hundred and forty two received two visits and 105 physicians gave their opinion on the visits through a questionnaire. Most (90%) respondents expressed a wish to receive an academic detailer on other topics, agreeing that two visits per year was a suitable frequency (Habraken 2003).

Another study used four, one to one visits between pharmacists and GPs in an attempt to increase the proportion of depressed patients taking antidepressants, and improve symptoms of

depression (Brown 2000). The intervention made a statistically significant difference on both outcomes.

In 2002, the Cochrane collaboration considered the importance of the number of visits on the effect of academic detailing (Thomson 2002). They reported a wide range, from once weekly for seven months (Steele 1989), to single visits (Newton Syms 1992), with examples of successful and unsuccessful outcomes across the spectrum. The review concluded on the need for standardisation and formal evaluation of the incremental importance of additional outreach visits.

The duration of effect after the last detailing visit is an important consideration, because the persistence of prescribing change will determine the extent of benefit incurred by patients. If it can be assumed that more frequent visits lead to a stronger and longer lasting effect, in designing a new intervention that builds on previous work, it makes sense to develop our understanding by increasing the number of visits and evaluating outcomes over a longer period. Therefore, the trial in this thesis tests the impact of three face to face meetings (as a balance between too few and too many) and evaluates outcomes over a longer period than any previous trials.

2.3.5.4 Overcoming organisational barriers to implementation

Organisational barriers are recognised as a key factor limiting the implementation of evidence based medicine (Haynes 1998). Some reports have highlighted practice or GP level organisational barriers as important factors limiting the introduction of prescribing change, but most investigators have not identified and addressed these prospectively. For example, none have set out to provide outreach visitors with the time and understanding to help practices with the additional effort needed to overcome organisational barriers. These might include patient identification, call and recall. A recurrent theme in the literature review thus far is that identification and addressing organisational barriers (at the level of the practice, the prescriber or the patient) is a key determinant of the success of detailing interventions.

While some detailing interventions incorporate strategies to explore and resolve GP level barriers, few apply this logic to practice level organisational barriers and fewer still to patient level barriers and supports.

Practice level barriers to implementation of (repeat) prescribing change can nullify or delay the detailer's efforts. If we assume educational messages are accepted, even if these are implemented on a patient by patient basis by GPs, completion of this task may take a long time in primary care, if the prescribing change applies to large numbers of patients. The administrative burden involved in patient identification and engagement, arrangement of consultations to facilitate prescribing then follow up, cannot be underestimated. Additional work can be expected for patients who do not attend pre-arranged appointments. Overcoming these barriers might involve the detailer helping the practice to identify patients who would benefit from changed prescribing and set up a register or recall system which systematically invites and appoints patients.

Moher tested this approach but not within a multifaceted, complex detailing intervention (Moher 2001). He compared the effectiveness of three interventions (audit and feedback,

recall to general practitioner and recall to nurse clinic) aiming to improve the cardiovascular assessment of patients in Primary Care. Establishing a nurse led call/recall system in practices and comparing the impact (for secondary prevention of CHD) on patients with CHD, they found that it was no better than audit as a means of promoting secondary prevention measures. Outcomes included reductions in blood pressure, blood cholesterol and continine levels. Each approach was found to be better than doing nothing, because assessment and follow up of patients was improved within intervention groups. The authors account for the inability of their interventions to deliver clinical improvements on GPs' unwillingness to initiate recommended preventative medicines including statins. If their practical support was accompanied by an educational exchange, this may have helped. They found that follow up by nurses appeared to be more effective than follow up by GPs.

In other UK based studies, systematic registration and planned recall of patients for appointments was found to improve the quality of care (Feder 1995; Pierce 1989), although there are now financial incentives for practices to systematically identify and treat patients with several common chronic diseases, including CHD.

An additional, often overlooked consideration in general practice which has a direct bearing on the chances of successful detailing outcomes is the accuracy and completeness of disease registers. These form the backbone of a successful call and recall system. Accounts of the accuracy and completeness of disease registers indicate variability (as expected) (Whitelaw 1996; Jick 1991; Lowrie 2005; Jick 1992; VanStaa 1994; Hassey 2001; Moher 2000). However, this evidence is not recent, and recognition of the need to improve the accuracy and completeness of disease registers and therefore reduce variation in processes of care has led to improvements, evidenced from the achievement on practices' GMS QOF points year by year.

If the aim of educational outreach is to improve the drug management of all eligible patients with the targeted condition, the detailer needs to be aware of the potential variation in the accuracy and completeness of practice level disease registers. Support should be offered to the practice to improve this, prior to introducing changes.

The UK based qualitative study by McColl further supports the idea that organisational barriers are important in the route to the implementation of evidence based medicine (McColl 1998). In addition, the attitudes and extent of teamwork within practices was seen as a major tension which has the potential to lead to a collective failure to agree practice level policies on clinical management, scuppering practice level changes in prescribing

Going a step further to involve patients and carers (in this case parents of children aged under 6 years old), Finkelstein (2008) studied the impact of an intervention combining detailing with posted, printed educational material directed at families. On comparing this approach with usual care, they found that the use of antibiotics diminished significantly in their intervention group. The authors concluded by emphasising the importance of involving patients/carers or the public in attempts to change antibiotic prescribing practice.

In healthcare systems where patients' ability to pay limits the uptake of health and related services, financial incentives for patients may be effective in overcoming barriers to changed behaviour (Benedetto 2000). Within the NHS these principles are unlikely to apply therefore will not be considered further.

2.3.5.5 Educational outreach plus additional strategies

As an example of how the detailing model has developed to include additional techniques, Brufsky conducted an interrupted time series study within a large health maintenance organisation covering four states in New England (Brufsky 1998). They compared a combined educational outreach and facilitation model to usual care, encouraging prescribing of Cimetidine instead of Ranitidine, for patients with gastrointestinal conditions. The prescribing of their preferred agent (Cimetidine), increased by 53.8% following the intervention. Other positive outcomes included an assessment of the rate of hospitalisations for gastrointestinal conditions. Their intervention proved effective and an accompanying economic analysis demonstrated cost effectiveness. Unfortunately, the intervention is not well described and for that reason, cannot be critiqued. The professional or other qualifications of those delivering it are also unclear, as are the content, duration, frequency of contacts, bespoke training received by people delivering it or the characteristics of patients and practices receiving it. Lack of information on these important features limits transferability. However, the authors assert that their combination of education and facilitation led to the successful outcomes. Facilitation included the use of bespoke forms to enable doctors to evaluate their own performance in relation to the prescribing of Cimetidine and the use of reinforcement strategies (e.g. feedback). In addition, the intervention team pre-screened lists of patients to clearly identify patients prescribed ranitidine who were appropriate candidates for Cimetidine. In this respect, the investigators employed marketing techniques and change methods not described previously or since then. Their methods resembled those used in everyday pharmacist prescribing support within general practices in the UK.

Nilsson and colleagues incorporated detailing with additional techniques to effect change, but unlike Brufsky, they stopped short of providing GPs with lists of patients who may have benefitted from changes to their prescribing for hypertension, peptic ulcer or dyspepsia (Nilsson 2001). Instead, they used patient level diagnoses and prescribing data from electronic patient records as part of their feedback. Feedback on prescribing rates, problem oriented educational outreach visits, educational material and the views of local opinion leaders were all used to encourage adoption of changed prescribing for the specified conditions. Within their randomised study which included three parallel intervention groups of GPs, they used before and after measures of prescribing change. Their intervention demonstrated a statistically significant improvement in prescribing.

Although New et al described their UK general practice based nurse led intervention as educational outreach, additional strategies were incorporated (New 2004). These included seeking the names of diabetic patients who were poorly controlled and providing these, together with the names of patients requiring review of their lipid and blood pressure management, to participating GPs. In contrast with Brufsky's study, New failed to achieve a statistically significant shift in their primary outcome of pre-defined targets for control of hypertension or hyperlipidaemia in patients with diabetes. In explaining this neutral result, organisational barriers were cited as an important limiting factor. These included apparent lack of additional activity within the practice, to review those patients with raised blood pressure and lipid levels. Already overburdened staff were resistant to accepting any additional work and some practices complained of a lack of resources to deal with the additional work. Practice nurses appeared more likely to support the outreach nurses than GPs but this dichotomy appeared to cause confusion among patients. Few practices have spare capacity,

ready to be deployed in this or any other way, without prior agreement or without reorganisation of existing staff or employment of additional staff.

The setting for the Brufsky study was within a US Health Maintenance Organisation. New set their study in general practice in the UK. Both studies were primary care based and utilised similar interventions, albeit within different methodologies. However, one major difference that is likely to have led to the different outcomes is the incentives of the staff for changing their prescribing behaviour. In the Brufsky study, staff pay was directly linked to cost effective prescribing and the investigators provided a rich vein of income to the practice on achievement of prescribing change. In the UK at the time of the study, improvements in control of blood pressure and lipids competed with management of other clinical conditions, pre-dating the introduction of the QOF. Prescribing in the NHS operates independently of direct market forces; therefore, additional financial reward is not a viable option.

The Cochrane Collaboration's findings would tend to support the effectiveness of the use of financial incentives for GPs (Gosden 2005). They evaluated whether payment of primary care physicians (capitation, salary, fee for service and mixed systems of payment) impacted differently on clinical behaviour and found that there was some evidence to support the case. However, detailing models and studies are difficult to compare across different healthcare systems, because there is the possibility that an invisible hand, i.e. payment systems, can significantly influence outcomes. It is difficult to account for this confounding other than through a multicentre study.

Recognising the need to help practices identify and target patients eligible for change, Feder et al used a combination of academic detailing together with disease register support. They demonstrated effectiveness in a cluster randomised controlled trial. They acknowledged the need to update disease registers as a pre-requisite to their detailing intervention and built their novel, multifaceted intervention on a sound knowledge and understanding of the context of the UK Primary Care and general practice system of organisation (Feder 1995).

Overall, there seems to be a reasonably strong logistical argument backed up by some published evidence, for incorporating a combination of strategies, including addressing organisational barriers in addition to the original cognitive approach described by Avorn and Soumerai. However, there is no 'off the shelf' description or standardisation of the components of this hybrid model and it remains to be tested in the context of a trial for patients with CHD or other vascular disease, in the UK primary care system, with measurement of longer term surrogate clinical outcomes.

Practice based prescribing support pharmacists are regarded as part of practice teams or, at least, the primary care team. Therefore, the pharmacists can support eligible patient identification, call and recall, and work in the practice for longer than other visitors. In so doing, the process of the original detailing model is developed to the point where the intervention offers a balance between educational exchange and facilitation of change through direct practical support to the practice. There are other examples of the application of prescribing support models combining educational outreach with additional strategies, but none involving the following: case identification, call and recall support, more intensive, repeated intervention with pharmacists working in practices on a weekly basis. Incorporating these features represents a necessary evolution in prescribing support, potentially providing a useful means of supporting prescribing decisions as the volume and complexity of prescribing for patients with LTCs continues to increase.

2.3.5.6 Cardiovascular disease focus

Attempts at improving targeted aspects of the management of cardiovascular disease in primary care through educational outreach or academic detailing, have generated positive results (Cupples 1994; Feder 1999; Jolly 1999; McCartney 1997; Seigel 2003). However, no studies have involved pharmacists, followed patients for longer than 1 year, focussed on statins, measured impact on anything other than prescribing or described their interventions or study populations in sufficient detail. Three of the most relevant are described in Table 2.4.

Table 2.4 Key features of selected studies

Authors/ Country/ Year	Method	Participants and setting	Interventions	Outcome measurement	Control	Effect on practice and patient	Comments
Avorn J, Soumerai SB. North America, 1983.	Cluster RCT	435 physicians from a Medicaid programme in 2 states of USA. Physicians selected on basis of high prescribing of \geq 3 target drug groups	Educational group of physicians received 2 visits from an academic pharmacist or pharmacologist over 6 months. Aiming to reduce prescribing of 3 drug groups.	Up to 9 months after intervention, measurement of number of units of drug prescribed across randomised groups.	Control and printed material only	Detailing on a one to one basis is effective and saves drug costs compared with printed materials only and control groups. Effect size: 18% drop in prescribing ($p < 0.0001$)	This trial was the first to implement a detailing programme and test it within a RCT. A market research consultant conducted interviews with non participating doctors, asking about their reasons for prescribing the 3 target drug groups. These insights were incorporated into the educational strategy. The pharmacist detailers made quantitative and subjective notes of their meetings. No information available on the characteristics of the pharmacist detailers, patients or physicians. No power calculation.
Freemantle, UK, 2002	Cluster RCT	75 general practices in 12 Health Authorities in England	Between 4 and 6 outreach visits by one of 12 community pharmacists who had received three days of training covering 4 clinical guidelines. Delivered the explicit techniques of academic detailing set out in Avorn and Soumerai's original work.	Change in prescribing of evidence based medicines advocated in the guidelines and in one case, alternatives. Secondary outcomes are changes in trends of medicines, collected by remote assessment of prescribing statistics without linkage to patients and diagnoses.	Control practices without education al outreach for 2 of the 4 guidelines .	5.2% improvement (95% CI 1.7% - 8.7%) in number of patients treated according to guideline recommendation. Smaller practices responded more favourably than larger practices.	Practices were given postgraduate educational allowances for participating, which limits generalisability and questions motivation for participation. The clinical guidelines were developed for the purpose of the trial. The results of this process are not likely to carry weight or support from participating practices because they were not involved in the production. No measure of prescription adherence or characteristics of patients at baseline. The authors concede that measurement of outcomes was complicated in each of the four clinical guidelines areas. Outcomes were positive for changes in 3 of the 4 guidelines; in the remaining guideline's educational outreach programme, a decrease in guideline prescribing with an OR of 0.73 (95% CI 0.56 - 0.94), equivalent to a 3% reduction in patients managed in line with the guideline.

Authors/ Country/ Year	Method	Participants and setting	Interventions	Outcome measurement	Control	Effect on practice and patient	Comments
Diwan, Sweden, 1995.	Cluster RCT	134 Health Centres in Sweden	4 meetings lasting 30 minutes each, over 5 months in the practice, group outreach by a pharmacist, covering guidelines on hyperlipidaemia management	Number of prescriptions for lipid lowering drugs and prescription of first line lipid lowering drug. Data collected from pharmacies including lipid lowering dose, strength, quantity. Age and sex were only demographics.	Usual Care	20% increase in prescribing of first line lipid lowering drugs (p = 0.03)	<p>Power calculation; stratification by number of prescribers and list size which is important as both can influence uptake of evidence. No measurement of cholesterol levels or adherence or clinical outcomes. No testing of model on single handed practitioners.</p> <p>This trial includes a larger number of physicians than any other published. Follow up lasted 1 year after intervention finished.</p> <p>No patient demographics other than age and sex; no clinical co-morbidities available.</p> <p>Consideration given to existing and incident patients receiving lipid lowering treatment.</p>

Studies involving pharmacists consulting with patients then making recommendations about changes to cardiovascular medicines were more common. One such study was conducted in 1997 in Hawaii. It was randomised, controlled, lasted 6 months and involved 94 patients, all with cholesterol of 6.2mmol/l or more (Bogden 1997). It involved one pharmacist discussing lipid lowering therapy, diet and behavioural modifications with patients and doctors in primary care. In the control group, patients received usual care from their doctor, without pharmacist intervention. Doctors retained responsibility for implementing the pharmacist's recommendations. The close interaction between doctor, pharmacist and patient resulted in a statistically significant increase in the number of patients with cholesterol levels below target and lower cholesterol levels among participants. The impact of the intervention was greater in the subgroup of patients with higher cardiovascular risk profiles (those with established disease and those with no established disease but with at least two coronary heart disease risk factors). The author attributed the success of the intervention to the initiation of lipid lowering medicines instigated by the pharmacist during the face to face encounter with the patient. Key discussion points were the likely importance of the aggressive nature of guideline implementation together with sustained positive rapport among physician, pharmacist and patient. The author also acknowledged the difficulty replicating their work in practice, because of the cost of the concerted effort to direct activities towards cholesterol lowering.

In the study by Latour (2000), the pharmacist encouraged physicians to decrease the prescribing of lipid lowering medicines for patients at low risk of vascular disease. The primary outcome was not achieved. The study design did not incorporate a control group, was quasi randomised, did not adequately describe the intervention characteristics and had a short follow up period of five months, all of which limits the strength of the evidence. However, this work stands out as one of the few that attempted to decrease the prescribing of a medicine that is unlikely to cause any harm if continued indefinitely. In fact, over time, as subjects' age, blood pressure and possibly other risk factors increase, it is possible that their cardiovascular risk profile reaches the point where a statin is indicated; this factor may have mitigated against the intervention working. The authors do not discuss this possibility. An important lesson from this work is the importance of carefully choosing the prescribing message to meet short term and long term patient and GP needs.

2.3.5.7 Pharmacy led educational outreach

This section considers lessons from the literature relating to pharmacist-led educational outreach, and considers direct implications for the new intervention to be tested in this thesis, which aims to improve statin prescribing.

In the UK, the concept of a general practice based prescribing facilitator/manager (distinct from pharmacist-led patient facing activities e.g. medication review) appears to have been first described by Leach in 1999. He suggested that to secure effective implementation of an agreed prescribing change at practice or population level, someone needs to take the initiative to modify practice computer systems, organise and send letters to patients. Since then, many different models of prescribing change have developed. In parallel, practices have developed an infrastructure that is now more able to absorb these changes e.g. the availability of practice nurses and practice managers, better trained reception staff and expert information technology solutions.

A Cochrane Review sought to answer the question of whether educational services delivered by pharmacists to physicians result in better outcomes (improved patient outcomes or decreased use or costs of health services) compared to the delivery of the same services by other healthcare professionals (Beney 2000). Insufficient evidence was available to answer this question, with only one controlled pre-post study cited. In this study, pharmacist-led delivery of outreach was compared with physician – led delivery. The objective was to reduce the prescribing of three contraindicated antibiotics and oral cephalosporin antibiotics. Physicians' educational support was found to be more successful, although more expensive (Schaffner 1983).

Newton Syms (1992) trained pharmacists to operate as detailers, using selling techniques normally associated with the pharmaceutical industry e.g. training on communication and presentation skills, approach to GP appointments, promotional aids. Pharmacists delivered non-commercial advice on non steroidal painkillers, individually to GPs working in single handed and group practices. Their trial compared prescribing from patients registered with GPs who had received the intervention and those registered with GPs who did not. The authors found a positive shift in the prescribing of targeted medicines. However, little information was available on the baseline characteristics of the GPs or patients and the study results are not presented in enough detail to enable critical appraisal of the analysis. It appears that the impact of clustering was not incorporated into the design or analysis which is likely to have led to overestimation of the significance of the observed effect. The follow up period was 5 months post intervention. Implications of this work for the educational outreach intervention and study described in this thesis, include the need to describe the intervention and pharmacists' training adequately, account for clustering and describe baseline characteristics of recruited practices and patients in sufficient detail.

In their design paper, Freemantle (1999) describe key features of their educational outreach intervention delivered by pharmacists across 48 practices in England but the extent to which support was targeted to call and recall was unclear. Outcomes included prescribing, summarised at practice level only. However, a lack of characterisation of patient demographics and prescribing at patient level, make interpretation of the impact of the intervention difficult.

One study involved community pharmacists in an attempt to improve the appropriateness of their recommendations for over the counter antifungal medicines. Community pharmacists received an educational outreach visit or attended a continuing professional education session (Watson 2002). This randomised controlled trial showed that there were no statistically significant differences in the appropriateness of antifungal sales from educational outreach.

In another UK based randomised controlled trial, community pharmacists delivered outreach visits to general practices (Watson 2001). The study intervention comprised posted guidelines combined with two, face to face outreach visits from community pharmacists, encouraging the prescribing of a limited list of three Non Steroidal Anti-inflammatory Drugs. Comparison groups were practices with and without posted NSAID guidelines. A useful description of the intervention included the duration of each outreach visit: up to 10 minutes was allowed, and visits were three to four months apart. Watson found no statistically significant differences were demonstrable in the primary outcome. From a theoretical and pragmatic standpoint, it is difficult to envisage how this very short contact time between detailer and GP would have enabled the change process to take place. Grol mentioned the need to achieve orientation,

insight and acceptance to encourage implementation of change in practice, all of which may take longer than two 10 minute slots in the context of a busy day (Grol 1992).

2.3.5.8 Pharmaceutical industry models

As with every other commercial, for profit organisation, the pharmaceutical industry spends vast sums of money on marketing. This includes supporting their representatives to engage with Doctors in Acute and Primary Care settings, disseminating promotional materials, staging conferences, carefully choosing research questions that promise to illuminate the benefits of their products in comparison with competitors, and provision of equipment to support diagnosis and prescribing. In 1994, an enquiry into the influence of pharmaceutical industry representatives on the NHS in the UK, estimated that the industry spent approximately £10,000 per GP annually on marketing. The amount spent by the NHS on delivering prescribing advice (which included pharmaceutical advisers) was approximately £500 per GP (National Association of Health Authorities and Trusts 1994). The industry makes best possible use of known influences on behavioural change. Much can be learned from their marketing techniques. For example, printed material used by representatives is often persuasive and visually appealing. Together with repetition of key points during brief opportunities, industry representatives are able to effect behavioural change in prescribing. Affability and the provision of updates, self declared “cutting edge” innovation in drug selection and small gifts all help to convey the message. Leaving free gifts may lead to an increase in the prescribing of company sponsored products, up to two years after the event (Schumock 2004; Glare 2006). In a review of the literature concerning interactions between doctors and pharmaceutical industry representatives from 1977 - 1993, Lexchin concluded that doctors’ prescribing behaviours are affected by their interactions (Lexchin 1993). This was found to be the case despite doctors’ lack of awareness of personal susceptibility to influence (Ruteledge 2003). To compound this finding, most GPs seem not to have a very high opinion of the information from pharmaceutical company detailers or company sponsored continuing medical education events (Lexchin 1993). This influence leads to increased prescribing costs (Brewer 1998), with one study showing that frequent general practitioner contact with drug industry representatives was strongly and independently associated with higher prescribing costs (Watkins 2003). However, there appears no reason why NHS pharmacists cannot adopt some of these techniques, although NHS pharmacists’ approaches are more limited in relation to provision of free gifts.

Although not clearly reported, the pharmaceutical industry occasionally enlists the support of local opinion leaders to advocate their products in the hope that they can persuade other physicians to prescribe. In primary care, prescribing is influenced by many factors. One influence for some GPs is endorsement of a medicine by a trusted consultant in secondary care, and prescription of a new medicine by a consultant leads to familiarity by the GP who has responsibility for ongoing prescribing. While the broad literature about the usefulness of local opinion leaders as a means of impacting on professional practice appears inconclusive, there may be some merit in this approach (Thomson 2005). On this basis, it appears worthy of inclusion in a multifaceted, novel prescribing support model.

Appropriate training appears instrumental to the industry’s success. It focuses less on pharmacology, more on communication skills: developing rapport, anticipating GPs’ needs, profiling individual GPs and highlighting drawbacks of competitors’ products. One study

explored the complex attitudes and behaviours of groups of GPs attending reflective practice sessions focussing on their prescribing. In commenting on the skill profile of the group facilitators (detailers), the authors asserted that effective group facilitation skills to create a group process were more important than a professional background and sound knowledge of therapeutics (Watkins 2004).

One study of the interaction between GPs and pharmaceutical company representatives, helped illuminate several marketing techniques used by the industry. These included “reciprocity” in which the GP is given a gift and in accepting, feels bound to make repayment, often through prescribing of the company’s product. As pharmaceutical companies and their representatives will show bias towards their own products, the authors recommended the introduction of a third party to provide unbiased educational information about the full range of medicines for specific conditions (Somerset 2001). Pharmacists, as NHS employees, particularly those working within the practice environment, seem ideally suited to this role.

Therefore, in designing a novel pharmacist-led outreach intervention for delivery by NHS employees, an awareness and use of techniques derived from pharmaceutical industry representatives and their training programmes, are likely to support uptake of new prescribing practice. The content of pharmacists’ training will be described in Chapter 3: Methods.

2.3.5.9 Targeted or untargeted outreach

In choosing who should receive outreach or academic detailing in a trial context, researchers usually choose to target those who have the greatest scope for improvement in the intervention. In the context of routine service delivery, the decision is likely to be guided by economic principles, which leads to the same, targeted approach, by offering a service to those who need support most, thus minimising inefficient use of scarce resources. However, the decision can be more complex, e.g. the equity dimension of whether a service should be offered to all or some. In addition, in primary care, rapid access to sufficiently detailed information may not be available to inform targeting e.g. how much unmet need is there in each practice in relation to maximum guideline doses of statins for eligible patients. Therefore, targeting may not be an option.

Soumerai and Avorn targeted high prescribers of inappropriate medicines with a view to decreasing prescribing (Soumerai 1990), and many other intervention studies since then have adopted the same strategy to maximise the chances of a positive result. For example, after exposing frequent prescribers of antibiotics to a 1:1 detailing session, there was a significant reduction in the number of days of inappropriate antibiotic usage in a large teaching hospital (Solomon 2001). Other evidence suggests delivery of academic detailing without targeting may lead to insignificant changes in the outcome of interest (Hall 2001). This observation is in accord with one of the barriers to implementation of change identified by the EBOR team (Nazareth 2002): lack of perceived willingness to change among prescribers.

However, untargeted detailing has the advantage of being more easily reproduced outwith the trial setting because it does not depend on the presence of prescribing outliers, who have a recognisable need to modify their prescribing towards the mean, and it does not rely on sufficient information to inform targeting.

2.4 Identifying and addressing weaknesses in research to date

In a systematic review of the effectiveness of pharmacists' activities on health service utilisation, costs and patient outcomes, it was concluded that more rigorous research was needed (Beney 2004). The following features were highlighted as important and in need of improvement in future work:

- Intervention definition and description;
- Health economic evaluation;
- Generalisability of the intervention (e.g. more pharmacists delivering the intervention rather than one or two highly specialist practitioners);
- Outcomes should include clinical events or surrogate clinical endpoints;
- Design and analysis to account for clustering

In designing the trial in this thesis, these features will be addressed as far as possible within the financial and time framework available.

Aspects of design are commonly cited as weaknesses in trials of interventions aiming to improve the professional or clinical decision making behaviour of healthcare professionals or patients (Hatoum 1993; Morrison 2001). Inappropriate designs or analyses are common and create difficulties in interpretation (Campbell 1998). Examples of this include inadequate sample size and bias in selection of practices (Avery 1997), absence of a control group (Field 1989; Green 1985; Wyatt 1992), lack of matching of controls and insufficient statistical analysis (Grant 1985), or lack of information on characteristics of the control group (Hill-Smith 1996). Studies with design weaknesses are prone to misinterpretation.

The literature review revealed the following recurring features needing particular attention.

2.4.1 Clustering

In primary care based randomised controlled trials in the UK, designed to study the effect of educational outreach, patient level randomisation is neither practical nor ethical. Randomisation by group (practice) is preferable because it avoids contamination of the usual care group and the effect of the intervention can be assessed in the natural practice environment. Using individual patient randomisation in an educational outreach intervention directed at general practitioners is not appropriate because the management of one patient is not independent of another (MacLennan 2003).

Some studies involve randomisation of health professionals or groups of professionals (cluster randomisation) but analyse outcomes at the patient level, thus resulting in a possible overestimation of the significance of the observed effects (unit of analysis error) (Whiting - O'Keefe 1984; Donner 1981; Donner 2000; Simpson 1995; Divine 1992; Donner 1990), without making corrections for the impact of clustering. Pill tested the impact of a patient centred intervention on GPs (Pill 1998). Twenty nine general practices were randomised and the results analysed at practice level; prescribing and other changes were measured at the level of the patient. However; analysis did not take account of clustering so the results are likely to be an overestimate of the significance of the effect.

Therefore it is important to build this learning into the methodology of a trial of a new intervention in primary care general practices, directed at GPs.

2.4.2 Pre-Randomisation and randomisation

Stratification (balancing influential variables other than the number of practices in each arm of the study) prior to randomisation is useful if there are characteristics of practices that make them more or less susceptible to changed prescribing.

In a trial of prescribing rationalisation in primary care in the Netherlands, Van Eijk assessed some key characteristics of practices prior to randomisation (Van Eijk 2004). Three characteristics independently influenced their main outcome measure: practices' use of prescribing feedback data, a formulary and a consensus on drug choice within the practice. Consequently, they stratified on this basis.

As there may be differences in the organisation, response to educational interventions and uptake of evidence based medicine between single handed and group practices, stratification by practice size has been recommended (Soumerai 1989). In keeping with this, Nazareth found disproportionately increased uptake of their outreach intervention in smaller practices compared with larger practices, supporting the case for stratification of this potentially important confounding variable (Nazareth 2002).

Van Eijk (2001) found more successful outcomes from group practice detailing, in their trial designed to compare the impact of both group and individual detailing on the use of highly anticholinergic antidepressants.

These two reports draw conflicting conclusions on the effect of detailing in group versus smaller practices. They perhaps underscore the relative importance of heterogeneity of context, intervention duration, delivery, intensity and topic on the outcomes, and the difficulties inherent in comparing different trials using similar interventions in different healthcare settings. This emphasises the importance of adequately describing these variables in order that other researchers and policymakers can compare with their own healthcare settings and draw their own inferences.

2.4.3 Recruitment and generalisability

A description of the process of practice recruitment in detailing type trials is useful because it enables an understanding of the representativeness of participating practices and informs the success of different recruitment methods, for other researchers.

Moher (2001) initially contacted eligible practices in writing. After two invitations, non respondents were telephoned to assess their willingness to participate. From 79 eligible practices, 21 (27%) agreed to participate and were randomised. Fifty eight practices did not respond to the initial written invitation, were not interested or had other reasons not to participate. It is not clear over how long recruitment lasted, how much resource was required to follow up non responders or whether non respondents were contacted in person.

Nazareth managed to recruit 75 of 102 eligible practices in their Evidence Based Out Reach (EBOR) trial (Nazareth 2002) however, further details on how they approached practices is lacking.

Van Eijk (2001), in common with most other trialists, do not describe their recruitment process. The lead investigator was known to the practices and it is likely that this helped.

Hall (2001) offered either a single outreach visit or audit and feedback to 38 practices in the intervention arm of a randomised controlled trial aiming to improve the drug based eradication of *Helicobacter pylori* infection in Primary Care. At the time of recruitment (1996), all practices in their catchment area were invited and ethical committee approval was not required. No detail on their recruitment process was given.

The transferability and generalisability of detailing studies is increased if the people delivering the intervention are less highly qualified, or representative of the majority of pharmacists practising in the community. Most randomised controlled trials involving pharmacists have recruited those with highly advanced training and postgraduate degrees (McMullin 1999; Lipton 1992). This drawback applies to the original pharmacist-led educational outreach work by Avorn and Soumerai in 1983, and, analogous to the targeting of outlying prescribers for intervention, specialists delivering outreach interventions will increase the chances of success, but reduces the generalisability of the results.

From an NHS perspective, using a more representative sample of the pharmacy workforce to deliver an intervention would increase the implementation potential. Therefore, an important consideration in designing the intervention is that the pharmacists have some additional training but are not so different from other prescribing support pharmacists that the intervention cannot be reproduced.

2.4.4 Choice and measurement of outcomes

Evaluating prescribing change in relation to set prescribing criteria generates a process rather than an outcome measure of quality.

In most studies involving guideline implementation, it is assumed that care is improved when a guideline is implemented. A direct, proportional relationship between prescribing change and guideline criteria might be assumed to result in improvements in quality of care. However without measuring health outcomes, it is difficult to confirm and quantify the effect size, yet a neutral or negative result from this type of intervention may represent an adequate response from the intervention but inappropriate guideline recommendations. Process outcomes may therefore be more appropriate for trials of health care delivery. They may be considered more sensitive indicators of quality than clinical outcomes because poor outcomes do not always result from poor processes (Brook 1996).

When there is a proven impact on clinical outcomes from improvement in prescribing in a clinical trial setting, it is likely to be specific to a particular health care setting (Thomas 2000). To date, there is insufficient evidence to link educational outreach visits to reducing the number or prolonging the time to hospitalisation or impacting on mortality. Therefore, evaluating the effectiveness of outreach visits in terms of clinical outcomes is desirable

(Thomson 2002). If this is not possible, surrogate clinical outcomes could be used, particularly in cases where there is a robust link between clinical outcomes and the surrogate end point, e.g. cardiovascular, cerebro- and peripheral vascular morbidity/mortality and cholesterol lowering or simvastatin prescribing.

On the other hand, it might be argued that given the unequivocal efficacy of some medicines e.g. Statins, it is an unnecessary duplication of effort to follow patients to the point where differences in clinical outcomes become apparent. 'Care as usual' as the control intervention is one acceptable way of dealing with this scenario.

One of the lessons learned from the cluster randomised controlled trial of educational outreach conducted by Gask (2004), included the usefulness of measuring patient level outcomes. Participating GPs received an educational intervention aimed at improving the process of assessment and management of depression. Patients with depression presenting to GPs who had received this intervention were evaluated for their depression status and satisfaction with consultations. The only positive outcomes in the study were patient reports of the improved ability of intervention group GPs to listen and understand their symptoms better. Most studies do not assess this type of patient oriented outcome.

The study by Solomon is also atypical in that it measured clinical outcomes. In their trial of antibiotic detailing in a hospital setting, they captured the impact on length of stay, intensive care unit transfers, readmission rates and in-hospital death rates. These were similar in groups of doctors receiving detailing and those with no support (Solomon 2001). However, their study was not powered to detect differences in any of these outcomes; the primary outcome was a reduction in prescribing of non-formulary intravenous antibiotics and this was achieved.

An unusual feature of the study by Nazareth (Table 2.4) was the choice of outcomes. The researchers evaluated three steps considered pre-requisites for the achievement of the primary outcome. The steps were general practice agreement to participate in the study, attendance at outreach visits and the GP's prescribing practice. While the trial did not show a statistically significant change in prescribing overall, their unusual choice of outcome measurement enabled a better insight to the reasons for the lack of impact, rarely seen in a randomised controlled trial design.

An additional consideration in the choice of outcome relates to whether new (incident) or established (prevalent) prescribing is evaluated at follow up. Very few trials evaluate both; most focus only on incident prescribing, presumably because it is a more sensitive indicator of effect and easier to measure. While this is a legitimate approach, it perhaps lacks the comprehensiveness of measuring both. A greater effect size is likely if a larger number of patients receive the targeted changes, which means all those patients who are eligible and already receiving medicines for LTCs should be considered suitable for prescribing change. In addition, measuring impact on both incident and prevalent cases is likely to be of more interest because both groups require support. As a demonstration of this point, in their trial of educational outreach aiming to reduce benzodiazepine prescribing, Zwar considered both, but detected a reduction over time in only the maintenance (prevalent) prescriptions for benzodiazepines (Zwar 2000). In contrast, GPs described more barriers when attempting to change maintenance treatments for asthma rather than incident treatments in one randomised controlled trial based in the Netherlands (Veninga 2000).

One study aimed to evaluate the impact of two different methods of implementing guidelines on the management of hyperlipidaemia. The comparisons comprised guidelines displayed in general practice case records in an algorithmic format or in a standard (non algorithmic) format. Unusually, prescribing or cholesterol changes were not evaluated. Instead, the authors chose to ask participants' opinions of their preferred guideline display and which method led to the most prescribing changes. A key finding was that there was a statistically significant mismatch between the perceived and actual proportion of patients managed appropriately between groups. However, as patient level and practice level prescribing data was not collected in sufficient detail, no more inferences can be made (Nguyen 2000).

Little is known about the longer term outcomes from detailing research. In the original trial testing academic detailing against passive dissemination of printed materials, the effect waned after nine months (Avorn 1983). Other evidence suggests effects weaken after 12 months (Pearson 2003) but no studies could be found where follow up lasted beyond 12 months. This argues for designing a study involving educational outreach with sufficient power to detect a difference in clinical outcomes over the longer term.

Figueiras (2001), showed that one to one detailing using reminders and focussing on only one (narrow) topic was effective up to nine months post intervention. Only two studies from thirty four identified through a systematic review in 1997 found that changes to clinical behaviour including prescribing were sustained beyond nine months (Beilby 1997). Until an empirical evidence base is clear, it could be argued that outreach visits are not the method of choice if longer term change is required (Tamblyn 1997).

The Anglia menorrhagia education study (Fender 1999), aimed to determine whether an educational package could influence the management of menorrhagia, increase the appropriateness of the choice of non - hormonal treatment and reduce referral rates from primary to secondary care. One hundred general practices were recruited within a randomised controlled trial. The intervention resembled academic detailing and the principles adopted by the independent academics were borrowed and acknowledged as being from Avorn and Soumerai's original work. Results were positive for two of the three outcomes: significantly fewer referrals and higher use of tranexamic acid but no decrease in the use of norethisterone in the intervention group practices compared with controls. While the trial was the first to use academic detailing in the area of menorrhagia management, the process for measurement of outcomes is a weakness in the trial design. GPs in both groups were asked to place a self report pad in a prominent place on their desks, and complete it following consultations with suitable patients. This approach ran the risk of under reporting for GPs within practices allocated to the control group who have not received any educational outreach support. There was no assessment, or reporting, of the true, or baseline, prevalence of menorrhagia across the practices. A practice computer search for prescribing of the implicated medicines and a practice Read code search for menorrhagia diagnosis before, during and after the intervention in each participating practice could have addressed this potential source of bias. It is also not clear whether the one year follow up period commenced at the second of two outreach visits or at some point thereafter.

Only one study could be found which was designed to explore long term outcomes from a detailing approach and a clinical endpoint. The trial design used historical and parallel comparator groups of practices; lack of matched controls and absence of randomised design limits the usefulness of the results (May 1999). However, doctors received intermittent visits

from detailers (pharmacists with teaching hospital experience) over a five year period, with the observation and data collection period spanning 11 years. With the outreach topic of 'safer prescribing of Non Steroidal Anti-Inflammatory painkillers', the research team from Australia measured the number of hospital admissions for gastrointestinal problems and found a profound (70%) reduction in the patients from practices continuing to receive outreach visits. What is surprising about this study is the magnitude of the effect: a 70% reduction over a long time period is an incredible achievement, but because of the way the researchers interacted with their GPs, is understandable. They gathered clinical and practice level evidence, weighed it up against other evidence, honed it by involving local experts and opinion leaders. Overall, a pragmatic study of this size is difficult to deliver, but due to the lack of randomised control group, the outcome remains uncertain.

Overall, it is preferable to measure clinical outcomes whenever possible and the longer the follow up the better, if we are to generate definitive evidence of the longevity of the detailing effect. Most work has not addressed either, therefore both will be considered in the present research.

2.4.5 Economic appraisal

Insufficient and inadequate economic evaluation of educational interventions creates uncertainty in the decision to adopt trials of implementation research with positive results (Brown 2002; Thomson 2002; Beney 2004). Based on available evidence, there is insufficient information indicating cost effectiveness. However, Soumerai evaluated the cost effectiveness of academic detailing within a randomised controlled trial and found it to be highly cost effective. Two meetings lasting approximately 18 minutes each, between a trained detailer and GP, were focussed on three drug groups commonly used inappropriately. They found that target drug use was decreased beyond the point where the model became cost effective. They also observed that the reduction was not affected by pre-intervention prescribing levels (Soumerai 1986).

Watson delivered educational outreach visits to GPs in England and found the costs of delivery were greater than the costs saved as a result of the (statistically insignificant) prescribing changes observed (Watson 2001). However, in this study based in 20 general practices in England, the team delivering the intervention did not explicitly make any recommendations of a cost saving nature which is unusual for pharmacist-led prescribing support in the UK. Without cost saving as one of the key outreach messages, and without an endpoint associated with significant costs (from an NHS perspective) e.g. hospitalisations, it is less of a surprise that cost effectiveness was unproven. May et al also found this to be the case in 1999.

Possibly the most detailed study of the cost effectiveness of outreach visiting was described by Mason (2001). Their perspective was that of the policymaker faced with the decision to implement guidelines on ACE inhibitors for heart failure and tricyclic antidepressants rather than newer, more expensive SSRI antidepressants. While their analysis, like the original publication (Nazareth 2002), is at times difficult to follow, it appears that their model of outreach became cost effective if the focus was on improving quality (increasing ACE inhibitor use in heart failure) but not for cost saving (tricyclic instead of SSRI antidepressants). Key reasons behind this were discussed and included the large health benefit

achievable through the use of ACE inhibitors in heart failure while the relatively small cost savings accrued by switching antidepressants did not offset the cost of the outreach visits. Acknowledging that the process of implementation of best practice in prescribing incurs a cost, Mason summarised the importance of evaluating the policy cost effectiveness of prescribing change models, and argued for the measurement of costs to form part of implementation research design.

2.4.6 The Hawthorne effect

The Hawthorne Effect was first described following attempts to improve productivity in the Western Electrical Company's Hawthorne works in North America in the 1920s (Mayo 1993). Subsequently, it was defined as 'an increase in worker productivity produced by the psychological stimulus of being singled out and made to feel important' (Franke 1978). More generally, the phenomenon of improved performance due to an awareness of being scrutinised or tested has been applied to participation in clinical research (Braunholtz 2001). In the context of clinical trials, it is not possible to control for the Hawthorne effect. In controlled trials involving educational outreach or other forms of support that cannot be masked by design, participants in the usual care arm are aware of their 'usual care' allocation and the fact that comparable participating practices are randomly allocated to receive an intervention. This may be enough to improve practice beyond that which might occur outwith the trial setting.

Not being able to control for the Hawthorne effect suggests educational interventions tested in a trial context, will appear less effective than they are in clinical practice. The literature review did not generate any information directly, about the strength of the Hawthorne in the context of educational outreach or other pharmacist led educational or prescribing interventions.

2.5 Template for a new intervention

Based on this literature review, and an understanding of the workings of repeat prescribing and general practices' approaches to disease management, the following are key features worth incorporating into the design and reporting of a multifaceted, new model of prescribing support:

- Utilisation of multiple strategies to effect change (Brufsky 1998);
- Face to face, brief educational exchanges with reinforcement;
- Adequate training for pharmacists, paying attention to communication skills and approaches used by the Pharmaceutical Industry (Lexchin 1993 and Watkins 2003);
- Clear definition of the components of the intervention and how they were delivered;
- Multiple intervention components including: anticipation of barriers, interactive provider education, confidential feedback, make explicit links between everyday practice and published evidence of effectiveness (Watkins 2003);
- Reminders, patient education;
- Specific focus on statin prescribing/cholesterol lowering;
- Involvement of local opinion leaders (Freemantle 2005);
- Intervention underpinned by theoretical models of behavioural change (Davis 1998, 1995);
- Delivery of the intervention to nurses and practice staff in addition to GPs (commonsense approach, recognising the dynamics of the general practice team);
- Minimum of three outreach visits, with sufficient time within each visit to establish rapport, credibility and inspire change (Yeo 1994);

- Confidential feedback on a one to one basis (Hux 1999);
- Twelve month duration of intervention with multiple meetings (Schmidt 1998);
- Provision of organisational and administrative help (Renders 2005);
- The use of pharmacists based in general practices (all previous work has involved community pharmacists or academics), with access to practice information and a peer support network between pharmacists delivering the intervention.

2.6 Template for a study to test a new intervention

Review of the literature spanning 20 years indicates that more and better evidence is needed to determine the effectiveness of pharmacists in their attempts to change prescribing behaviour. The available literature is difficult to interpret because of inconsistent or nonexistent nomenclature or explanations of the interventions delivered by pharmacists. Study designs are often inadequate, trial durations and length of follow up insufficient to enable evaluation of clinical outcomes and much of the outcomes are process related. Other trials have methodological weaknesses such as lack of control groups, poor methods of randomisation, inadequate statistical analysis and problems with internal or external validity (McLaughlin 1991; Beaudry 1989).

The following features of a trial are therefore likely to add to the body of literature in this area:

- Sufficient power to detect differences in clinical or surrogate clinical outcomes;
- Applied across different general practice settings (affluent, deprived, single handed, group practices, training and non training (while it is unlikely that statin prescribing patterns differ between training and non training practices (Ashworth 2006, Mackay 2003), we considered it useful to have recruited both types of practices with examples in each arm of the study);
- An assessment of prescription collection rates as an indication of the extent of adherence to newly prescribed medicines;
- Recruitment of untargeted practices, where there is variability in the need for changed prescribing (this will help confer generalisability of the results);
- Stratification of important measures of baseline prescribing;
- Pilot work to ensure theoretical underpinning, feasibility of the model including acceptability to GPs;
- Appropriate choice of methodology and analysis to take account of clustering;
- Description of qualifications and training of pharmacists delivering the model;
- Collection of patient and practice level prescribing data at baseline and follow up, including incident and prevalent cases;
- Follow up of outcomes after 12 months (Pearson 2003);
- Link any cost savings to health outcomes (Belby 1997).

2.7 Summary

In view of the increase in LTC prevalence and the increased cost and complexity of prescribing, introduction and testing of a new prescribing support model is timely. The publication of HPS in 2002 signalled a change in the management of cholesterol and vascular risk using statins (HPS 2002). The message was that all patients with established occlusive arterial disease were at high risk and should be treated with a statin, regardless of total blood cholesterol level. In Glasgow, this recommendation was disseminated passively by post to each general practice in the form of an updated clinical guideline (Appendix VIII). In view of the potential importance of this updated guidance to the local population and the relative ineffectiveness of passive dissemination as a means of changing prescribing practice, it was appropriate to test a new intervention to improve statin prescribing for a high risk cohort of primary care based patients. Priorities included constructing, delivering and testing a novel educational outreach intervention with the objective of changing healthcare professionals' prescribing behaviour relating to statins or the management of vascular diseases in a way that enabled measurement of outcomes of benefit to patients.

Herbert (2004) summarised the need as follows: "Clear messages, proper trial design and sensitive outcomes are necessary to demonstrate changes in prescribing".

General practice based pharmacists will be trained to deliver this intervention, as they are ideally placed to implement guidelines in the long term, as part of their routine service delivery.

Chapter 3

Methods

3.1 Background

This chapter justifies and describes the methodology of a cluster randomised controlled trial of a new, pharmacist-led intervention called Statin Outreach Support (SOS).

3.1.1 Complex interventions and their evaluation

The Medical Research Council's guidance on developing and evaluating complex interventions describes dimensions of complexity and the implications for evaluation (Medical Research Council 2011). The SOS intervention constitutes a complex intervention on the basis of several dimensions of complexity:

- Number of interactions between components in the experimental and control interventions;
- Number, and level of difficulty, of behaviours required by those delivering or receiving the intervention;
- Number of groups or organisational levels targeted by the intervention;
- Number and variability of outcomes;
- Degree of flexibility and tailoring of the intervention permitted.

Consequently, the guidance recommends several features worth considering in an evaluation programme. Of relevance to the SOS trial are usefulness of a range of outcome measures and the suggestion to adapt the intervention to "a local setting" (in this case, practices).

Using the learning from Chapters 1 and 2, describing the following features is important to enable comparison with previous work, and will be addressed in this chapter:

- Number of visits and other contacts;
- Duration of visits;
- Timing;
- Objectives of meetings;
- Description of those present in the meetings;
- Nature and duration of preparatory work and follow up support;
- Level of access to patient information;
- Clinical topic(s) considered and main messages delivered;
- Extent to which the pharmacist identified organisational issues in addition to personal barriers relating to knowledge/beliefs;
- Extent to which the pharmacist supported the practice or GP to implement change;
- Rationale for choice of outcomes.

3.1.2 Rationale for using a cluster randomised controlled trial design

Poorly defined educational outreach interventions and methodological weaknesses in associated trials are common; a Cochrane review has recommended improvements in both (Thomson 2002).

Cluster trials are an important method of evaluating educational outreach and related interventions, but cluster randomised trials may be more difficult to design and perform than individually randomised trials, because of the threat of bias (Puffer 2003). There are opportunities for bias at cluster and individual patient level. In addition, the choice of cluster design brings a requirement for increasing the sample size. Therefore, the choice of cluster randomisation design was considered carefully.

The questions to be answered by this trial were whether (and if so, the extent to which), the SOS intervention, delivered at practice level, increased the proportion of community dwelling patients receiving a statin at optimal dose, with cholesterol controlled (less than 5mmol/l (less than 4.2mmol/l post Coronary Artery Bypass Graft; Appendix VIII). These questions were best answered through a prospective, randomised controlled trial design with sufficient follow up to enable the effect of any improvements in statin prescribing and cholesterol levels to develop.

Practical reasons led to the decision to use cluster randomisation. During a pilot in five practices in 2002 (and extensive pre-pilot work in the years prior to that), the SOS intervention was found to be best suited for delivery at general practice level, because practice level organisational barriers were recognised as rate limiting when pharmacists attempted to change statin prescribing. For example, if one or two GPs or nurses within a practice were motivated to systematically identify and offer eligible patients simvastatin 40mg, this might not translate into action because the other GPs and nurses needed to be supportive and share the workload. Agreement from all GPs and Nurses was necessary to enable identification of eligible patients and co-ordination of the process of patient invitation and follow up. Targeting and randomising individual GPs for an educational and organisational support intervention was therefore impractical, as was maintenance of blinding between GPs in the same practice. Contamination through exchange of learning between GPs from the same practice was unavoidable; and contamination of usual care leads to biased estimates of effect size (Ukomunne 1999).

Randomisation at patient level was not appropriate either, because responsibility and prescribing decisions for individuals were subject to change and influence by multiple GPs and Nurses over the course of time. This meant that the prescribing and cholesterol management of patients in one practice were more similar to each other than patients from another practice. This violates the assumption of independence necessary for an individually randomised trial (and the assumption of independence of observations).

Prospective, cluster randomisation offered the best way to eliminate these threats of systematic error (Campbell 2001).

The need to account for clustering extended to most aspects of this trial: randomisation, sample size estimation and power, analysis and reporting. Campbell (2001) suggested describing these and other items separately, when reporting a cluster randomised controlled trial. Their checklist of items will be used in this chapter.

3.2 Methods

3.2.1 Setting - NHS GG&C

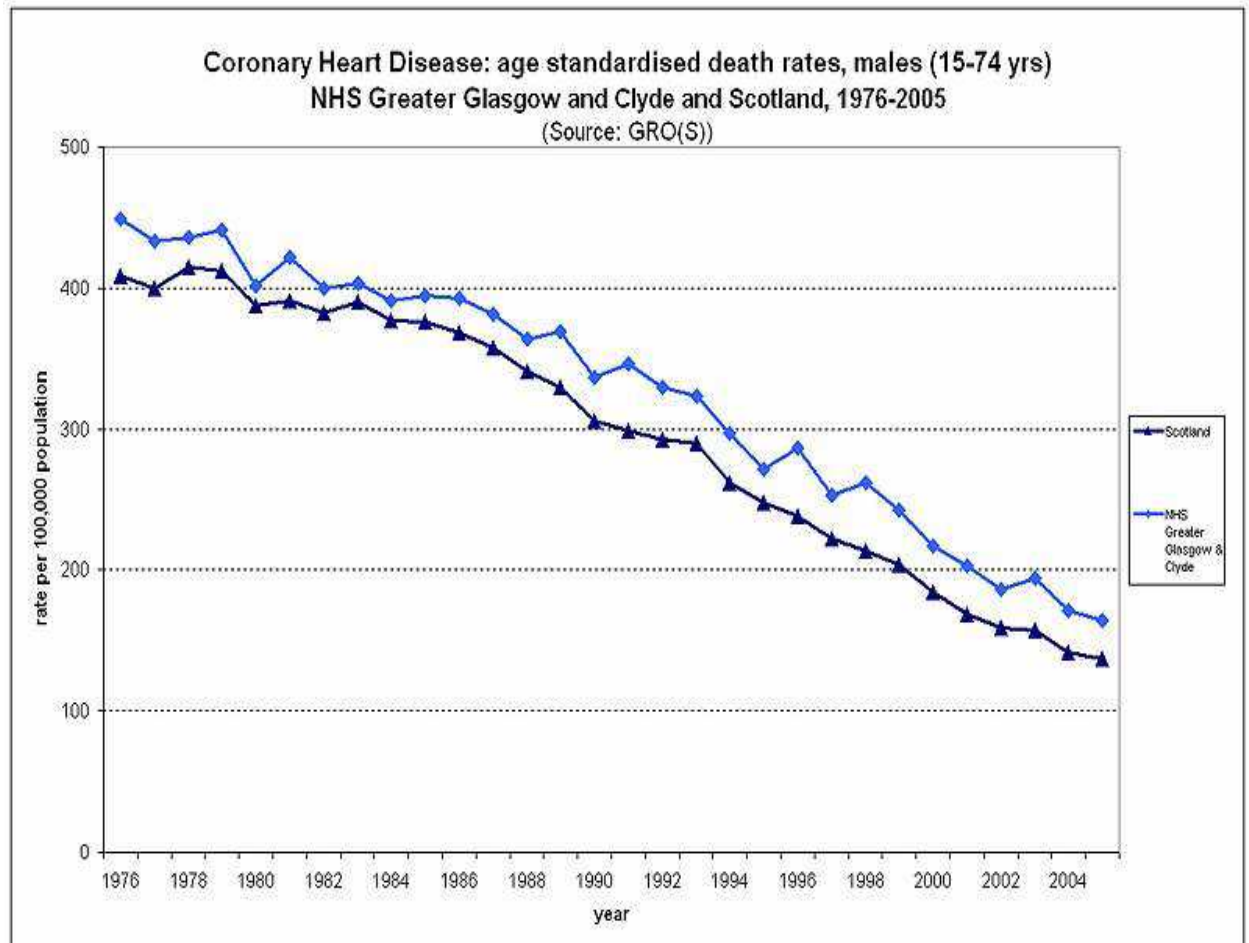
At the start of the SOS trial (2003), NHS GG&C existed as two geographically and organisationally separate Board areas: Greater Glasgow Health Board and Argyll and Clyde Health Board. In 2006, Argyll and Clyde Health Board split and the Argyll area merged with Highland Health Board. Greater Glasgow Health Board absorbed the Clyde component, and was renamed GG&C Health Board. The SOS trial involved practices and policies within Greater Glasgow only.

NHS GG&C Health Board provides health care to almost 25% of the Scottish population. The GG&C population lives within a diverse geographical area, encompassing both urban and rural settings and suffers high levels of deprivation and unemployment with the worst health status and most extreme health inequalities in Scotland. Although overall life expectancy is increasing, the population faces a growing burden of morbidity and disability driven by LTCs. In addition, the Board area continues to attract an increasing migrant population, with their own health challenges. LTCs account for over 80% of total general practice consultations and 60% of hospital bed days (Department of Health 2004). Cardiovascular Disease (CVD), cancers and chronic respiratory disease account for the majority of premature deaths. In the Board's Director of Public Health Report (2009), the following key health problems were identified:

- CVD;
- Health inequalities;
- Substance Misuse (drugs, alcohol and smoking);
- Obesity.

A substantial proportion of CVD risk is attributable to high cholesterol and some of this is preventable through prescribing of statins in accordance with robust evidence from clinical trials. CVD encompasses several distinct conditions e.g. Coronary Heart Disease (CHD). Other conditions sharing the same vascular pathophysiology include stroke, Transient Ischaemic Attack (TIA), Peripheral Vascular Disease (PVD) and Diabetes. Underlying coronary vascular disease is the most common reason for Coronary Artery Bypass Graft (CABG) and Angiography, which classifies patients who have undergone these procedures as being at equivalent risk as patients with CHD. CHD is the largest subgroup of CVD and as such, is a strong predictor of CVD trends. A summary of the combined prevalence and impact of vascular disease within GG&C was not available. However, age standardised CHD death rates were available and are described in Fig 3.1. While the prevalence of CHD is decreasing, in GG&C Health Board it remains the leading cause of death, with rates consistently above the National average (Figure 3.1).

Figure 3.1 Coronary Heart Disease Death rates in NHS GG&C



Several factors could have accounted for the steep decline in death rates in GG&C and the rest of Scotland over this period. These include improved primary and secondary prevention of CHD e.g. improved prevention and management of hypertension or myocardial infarction (Capewell 1999). Decreases in blood pressure over this period were confirmed by data from the Scottish Centre MONICA studies, with additional data showing reductions in smoking prevalence and cholesterol levels between 1976 and 1996 (Evans 2001).

The Heart Protection Study and derived GG&C guidance offered an opportunity to further tackle the burden of CHD and other vascular mortality for patients with vascular disease, because of the finding that simvastatin 40mg daily for 5 years reduced the rates of heart attack, stroke and revascularisation by approximately 25%. While cholesterol decreased in HPS, the use of simvastatin 40mg was sufficient to achieve benefit without cholesterol reduction.

The challenge for GG&C and other health care providers is to maximise the uptake of robust evidence based treatments such as this.

3.2.2 Aim of study

The aim of the study was to evaluate the effectiveness of pharmacist-led SOS intervention delivered at the level of general practices, to practice staff.

The SOS study therefore tested the hypothesis that primary care, general practice based pharmacists delivering the SOS intervention at practice level, can increase the proportion of patients prescribed simvastatin 40mg with their cholesterol controlled, compared with care as usual.

3.2.3 Endpoints

The primary endpoint was the proportion of patients prescribed simvastatin 40mg daily with cholesterol controlled, evaluated at the level of the individual patient, in the SOS intervention arm practices compared with Usual Care (UC). Secondary endpoints were:

- Prescribing of simvastatin;
- Cholesterol control;
- Prescribing of simvastatin 40mg;
- Cholesterol tested since randomisation for patients prescribed simvastatin 40mg;
- Cholesterol levels of patients prescribed simvastatin 40mg;
- Cholesterol levels tested since randomisation;
- Cholesterol levels;
- Prescribing of any statin.

Outcomes were assessed between 1.4 and 2.2 years (mean 1.7 years) after randomisation.

In a post hoc analysis we assessed the impact of the SOS intervention on safety outcomes using the time to first vascular event, for those patients who could be traced from baseline to follow up. The mean duration of follow up for safety outcomes was 2.5 years, ranging from 2 to 2.8 years.

3.2.4 Sample size and power

Cluster randomised trials require larger numbers of individuals because there tends to be correlation of outcomes within clusters which otherwise reduces the statistical power, compared to individually randomised trials. The method of calculation of sample size is a key difference between a practice randomised trial and an individually randomised trial: the sample size needs to increase to accommodate clustering, using a cluster inflation factor (also called the design effect, D). The design effect is related to the cluster size (m, the number of patients in each cluster) and the intra cluster correlation coefficient (ρ , which measures the size of the clustering effect i.e. the correlation of patient outcomes within a cluster) by the equation:

$$D = 1 + \rho (m - 1)$$

The design effect enables calculation of the amount by which the sample needs to be multiplied, to maintain sufficient power.

The original sample size calculation for the SOS trial was based on a pilot study in five general practices in 2002. Then, the intervention was planned to focus on statin prescribing for patients with CHD only. We found that approximately 50% of patients with CHD had controlled cholesterol before the intervention. For patients with no record of cholesterol level recorded in their case notes, we assumed cholesterol was uncontrolled. There was considerable variation between practices, with $\rho = 0.4$. We assumed that 40 patients would be recruited per practice in the subsequent cluster randomised controlled trial, demanding a sample size increased using a design effect of 16.6 ($D = 1 + 0.4 \{40 - 1\}$). On this basis, it was calculated that approximately 20 practices (10 per group) would be required for the study.

Pilot work also showed that 80% of patients with CHD and uncontrolled cholesterol would achieve cholesterol control after the SOS intervention (resulting from increased prescription of simvastatin 40mg). Assuming the proportion of CHD patients controlled in intervention practices would be 90%, compared to 50% in control practices, and that 40 patients were selected from each practice, then a study with 10 practices in both the intervention and control groups would have in excess of 90% power to detect this difference at a 5% significance level. If 30 practices were selected (15 in intervention arm and 15 in UC arm) this would allow for up to five pairs to drop out of each arm of the study. The high practice dropout was anticipated in view of the duration and intensity of the intervention, which was considered difficult to sustain, from practices' perspectives.

Recruitment secured the participation of 31 practices. At baseline, data were collected for a greater number of patients than anticipated (mean of 130 patients per practice). This was due to requests by practices, who were keen to use the data for audit purposes, irrespective of subsequent allocation. All practices therefore accessed their baseline information, as collected by the pharmacist. We found approximately 40% of patients had cholesterol controlled (Appendix VII). These findings led to a lower design effect of 7.45, and enabled re-calculation of $\rho = 0.05$ (Ridout 1999). The study was therefore powered to detect much smaller intervention effects than anticipated from the pilot. For example, assuming 88% of the intervention group would have cholesterol controlled at the end of the intervention period (Dec 2004) compared with 76% in the UC group, the study had 93% power to detect a difference in cholesterol controlled between groups at a 5% significance level.

Ethical approval and study registration

Ethical approval was granted in December 2002 (Appendix VI). At that time the intervention was called 'clinical facilitation' and a cost effectiveness analysis was planned to run in parallel to the study. As the unit of intervention, all practices provided written consent to participate. The study was registered: ISRCTN61233866.

3.2.5 Practice recruitment

All 232 single handed (SH) and Group (G) practices in Greater Glasgow (population 962,106) were eligible to participate and invited as follows:

1. The NHS Glasgow register of general practices was separated into SH (one GP listed against the practice cipher number, $n = 63$) and G practices (more than one GP listed against the practice cipher number, $n = 169$). Each practice's CHI code was entered into MINITAB and random numbers generated. Forty eight practices (24 single handed and 24 group) were randomly selected to obtain 30 consenting practices.

2. Each practice was contacted by phone to confirm the names of the GPs, practice manager and nurse(s). Although the register of practices was the most accurate available at that time, seven single handed practices were no longer in existence: six had dissolved and one had merged with a group practice. Therefore, eight additional SH practices (seven replacements and one additional in view of the rate of dissolution of single handed practices at that time) were randomly identified for invitation purposes.

3. A draft invitation letter was passed to 4 practising GPs and the study supervisor (JM) for comment. Suggestions for change were incorporated and every GP, nurse and Practice Manager in each practice was posted an invitation to participate. A reminder was sent if no reply was received from the practice within two weeks.

4. If no reply was received, after a further two weeks, another invitation was sent.

5. Non responding practices were phoned and asked for a decision. Three SH practices did not reply in writing, but were keen to meet to find out more information before deciding. Two subsequently declined and one consented after meeting. One Group practice requested a meeting prior to deciding. At the meeting, the practice consented.

6. On receiving written practice consent to participate, a meeting was arranged with each practice, to provide adequate information about the study to confirm all practice staff understood the study requirements and to minimise dropout.

The invitation process was approached systematically, so as not to favour selection of one practice over another and minimise this potential source of bias. Thirty one practices (15 SH and 16 G) representing a total population of 116,558 patients, (12% of the Glasgow population), agreed to participate. All practices routinely recorded patient demographic, clinical and prescribing information on their computerised administration support system.

3.2.6 Participating practices and patients

3.2.6.1 Practice staff

All Practice staff (reception staff, practice managers, GPs, Nurses and any other staff) received a verbal reminder of the intervention and usual care arms of the study, from the pharmacist collecting baseline data.

3.2.6.2 Eligible patients

Practices were asked to identify patients who had confirmed vascular disease. These patients were at $\geq 30\%$ risk of suffering a cardiovascular, cerebrovascular or peripheral vascular event in the next 10 years. In accordance with GG&C Cholesterol Guidelines (Appendix VIII), this level of risk was confirmed by the following confirmed diagnoses:

- Myocardial infarction;
- CABG / angioplasty;
- Angina;
- Angiographic coronary artery disease;
- Stroke/transient ischaemic attack;
- Peripheral ischaemic arterial disease/intermittent claudication;

- Diabetic patients aged over 45years.

A validated computer search of each general practice's computerised patient record generated a list of eligible patients. The validity of the computer search was evaluated during the pilot phase in two practices (Lowrie 2005). Sensitivity (completeness: how good the search was at identifying patients with a confirmed diagnosis of vascular disease recorded in the case notes) ranged from 88% to 100% and positive predictive value (the chance that patients identified by the search have a confirmed diagnosis of vascular disease) ranged from 63% to 66%. This lower than expected positive predictive value led to the decision to screen each patient's handwritten case records to collect relevant data in addition to collecting data from computer records.

3.2.7 Baseline data collection

The following baseline data was collected by NHS employee pharmacists between May and November 2003, across all 31 practices:

Practice characteristics	Demographic field	Qualifying diagnoses§	Drug field
List size, Post code	Practice CHI	MI	Statin (description of which statin) Dose
Number of whole time equivalent GPs	Date of data collection	Diabetes, CABG	Start date
Number of whole time equivalent practice nurses	Patient identification number	Stroke Angioplasty	Dose increase date
Number of patients at \geq 30% 10 year risk of suffering a cardiovascular, cerebrovascular or peripheral vascular event	Date of birth	TIA, Angina/IHD	Most recent cholesterol level
	Sex	PVD/Intermittent claudication	Date of most recent cholesterol level
	Patient status (left practice, case notes unavailable)		

§with accompanying date event(s) / diagnoses first recorded on practice computer

The template used for baseline data collection is given in Appendix IX. Due to time and resource limitations, a systematic sample of every third eligible patient's data was collected in 5 practices with the largest list sizes (12330, 7354, 7215, 7099 and 5616 patients). Therefore, cross sections of data were collected at baseline. In addition, in all practices, some demographic data (in particular, the "Patient identification number") was not collected. Both factors precluded longitudinal follow up of all patients. In all other practices, data was collected from each eligible patient's record, anonymised in the practice and entered onto an ACCESS database.

3.2.8 Randomisation

3.2.8.1 Sequence generation

Due to the relatively small number of recruited practices and practice level randomisation, only two strata were used (Pocock 1983). To maximise the chances of practices in the intervention and UC arms of the study being comparable at baseline, we separated practices into the prognostic factors that were thought to impact on the primary endpoint: Single Handed (SH, n=15) or Group (G, more than one full time GP; n=16) and the proportion of eligible patients whose cholesterol was controlled at baseline. This distinction was made because we suspected that larger practices were more likely than single handed practices to implement the SOS intervention. Though we were not aware of an evidence base surrounding this (in fact, the results from the EBOR trial suggest the opposite (Nazareth 2002), however, we suspected that Group practices would have three features favouring better uptake of the SOS intervention:

1. Multiple partner practices would have more advanced record keeping, systematic case finding, call /recall systems;
2. Greater capacity and flexibility to absorb additional work incurred by the intervention;
3. More spare rooms, enabling a pharmacist to work with the practice team on the same day each week. This would tend to increase the chances of the intervention working.

To minimise imbalance between SOS and UC practices in proportions of patients with cholesterol controlled, our framework had this as a secondary division. We used the ratio:

$$\frac{\text{Number of eligible patients with cholesterol in target range}}{\text{Number of eligible patients}}$$

Within their strata (SH or G), practices were arranged in ascending order according to this ratio, ordered then numbered sequentially, and paired (practice 1, practice 2), (practice 3, practice 4) etc.

This approach to randomisation minimised the differences from these prognostic factors, between treatment groups, to validate the assumption that any differences seen in the outcomes were most likely due to differences between the SOS intervention and UC and not random imbalances in baseline characteristics between practices in the SOS and UC arms.

3.2.8.2 Allocation concealment

A table of random numbers (MINITAB statistical software) was used with one practice from each pair randomly allocated the number “1” and the other allocated “0”. The SOS intervention group was randomly allocated “1” and UC, “0” (Appendix X). This process sought to ensure a balanced allocation of practices between SOS and UC arms in respect of Practice status (SH or G). This type of matched cluster design (‘matched pair’ in which one of two matched clusters in a stratum are randomly assigned to each intervention) is frequently adopted in cluster randomised trials (Donner 2000). The allocation was therefore based on clusters rather than on individuals, and the identity of all the practices was concealed until after allocation to SOS intervention or UC.

3.2.8.3 Implementation

The allocation sequence was generated by Alex McConnachie (AMcC). Richard Lowrie (RL) assigned practices to the SOS intervention or UC. Randomisation and random allocation took place on 4th November 2003, resulting in 8 group practices allocated to the intervention group and the corresponding 8 practices allocated to UC. In the single handed practice stratum, 6 pairs were formed and one from each was allocated to the intervention/UC group. One SH triple was formed with two practices allocated to the SOS intervention and one to UC. However, on contacting the practices to notify them of their allocation to the SOS intervention or UC status, we found that one SH practice had already disbanded (this practice was one of the triple and had disbanded, unknown to us at the time, before the date of randomisation). This practice's patients were dispersed across other Glasgow practices and could not be followed up. Therefore this practice's patients were not included after baseline description of collected data.

Sixteen practices (8 G and 8 SH) were allocated to the SOS intervention arm and 15 practices (8 G and 7 SH) were allocated to the UC arm of the study. Progress of practices and patients through the initial stages of enrolment and allocation is described in Appendix XV.

3.2.8.4 Blinding

In common with trials of other educational interventions, double blinding was not possible. The study was assessor blind, because when data was collected at baseline, allocation had not occurred. At follow up, two independent researchers collected prescribing and cholesterol outcome data. Both were blinded to whether practices had received the SOS intervention or UC, therefore bias in the process of data collection was minimised.

3.2.9 Statistical analysis

Baseline analysis compared participating with non-participating practices, SOS with UC practices, and single handed with group practices. Patient level data was not collected for non-participating practices. Summaries used continuous and categorical variables, as appropriate. Practice-level data (e.g. number of GPs, list size) was compared using the Wilcoxon-Mann-Whitney test, or, for comparisons between SOS and UC practices, using the Wilcoxon Signed Rank test within pairs of practices.

Patient level data were analysed at the individual level for greater power. Analysis of primary and secondary endpoints involved the use of regression models, to account for pairing. Each outcome was dependent upon whether or not an individual was in a SOS or UC practice, and on which practice pair they were in. The regression models therefore included an adjustment for the matching used in randomisation, in the form of a 15 level categorical variable with each outcome being dependent upon whether or not an individual was in an intervention or control practice, and on which practice pair they were in.

Logistic regression was used for binary (categorical) outcomes e.g. male/female or qualifying diagnoses and normal (least squares linear) regression was used for continuous outcomes e.g. age. For comparisons of cholesterol levels, a (natural) log transformation was used due to the skewed distribution and back-transformed for reporting purposes.

For comparisons between single handed and group practices, data were aggregated up to practice level and compared using the same methods as for practice-level data.

This approach was used instead of chi-square or t-tests, because of the need to adjust for the matching of practices.

Subgroup analyses of the primary and secondary outcomes were: age, gender, practice level socioeconomic deprivation, practice type, patients eligible at baseline vs. eligible after baseline, cholesterol controlled at baseline vs. uncontrolled at baseline, statin prescribing at baseline, number of vascular diagnoses at baseline, presence / absence of CABG at baseline. A two-sided p-value of 0.05 was taken to represent statistical significance in all analyses. RL conducted all analyses (at baseline and follow up) using MINITAB version 13. Confirmatory analyses were conducted by The Robertson Centre for Biostatistics (Suzanne Lloyd, AMcC).

Fixed and Random effects models

There were multiple measurements from the same practice and pair. Regression analysis was used to investigate the relationship between the response variable and one or more predictors. Fixed effects regression models assumed the only source of variability was between subjects (and that this was constant across all practices); adjustment was made only for the pairing of practices. However, the data was not independent (patients within practices and pairs were more likely to be similar to one another than patients from different practices and pairs). Random effects regression models treated practice pairs as random effects, taking into account two forms of variability: within practice/pair and between practice/pair variability.

Either fixed or random effects models could have been used; both were tried, and the results were very similar, with fixed effects being reported. In each case, models were adjusted for age, sex and deprivation in addition to the pair.

3.3 The SOS intervention

Appendix XI summarises the process of the SOS intervention. This summary was used as an aide memoire by practice staff. Pharmacists delivering the SOS intervention introduced, discussed and reinforced the main messages from this guideline during three face to face meetings. Between meetings, the pharmacist worked in the practice one day per week, to understand and whenever possible, improve the practice's attempts at introducing a systematic approach to offering simvastatin 40mg to eligible patients.

3.3.1 Overview

Face to face meetings involved GPs, nurses and non clinical (administrative) staff in 15 of the 16 practices. One practice (Single handed), participated in the first meeting but then the GP declined further meetings due to time constraints. All intervention arm practices received meetings on different dates, but all three meetings were completed between December 2003 and December 2004. The gap between meetings was approximately 4 months, depending on the availability of the GPs, size of the practice and pharmacists' annual leave. The names and contact details of eligible patients (who were not prescribed simvastatin 40mg) were identified by the pharmacist and practice staff. The pharmacist

helped the practice to agree on whether, how and when to introduce a new prescription for simvastatin 40mg to eligible patients, on a case by case basis. GPs were asked to adopt and apply the same approach to statin use (i.e. guideline based) for incident patients as they encountered them during routine practice.

Before the first meeting

Pharmacists worked in their allocated practice one day each week for approximately one year. They accessed, collected and summarised patient level information to confirm that each patient who was eligible for a statin had been offered one, or was currently prescribed a statin. This involved confirmation of eligible diagnoses, statin prescribing (current and historical), prescription ordering, cholesterol tests and levels. Practice disease registers were validated and updated or amended where necessary. Objective or subjective confirmation of diagnoses was sought by looking through case notes, computer records or hospital (including Accident and Emergency) discharge letters.

The pharmacists collected the names of eligible patients who had no history of having received a statin or who were prescribed a statin at a dose lower than 40mg simvastatin equivalent. If there were any obvious reasons for the patient not having a statin at sufficient dose, this was collected. Reasons for patients not receiving a statin included failure of the practice to offer one, the patient defaulting routine appointments, dropout from prescription ordering or a history of statin intolerance or contraindication. Some eligible patients had been overlooked by their practice; the pharmacist reinstated these cases onto the relevant disease register, in order that they would be subject to routine call and recall for review by the practice, or contacted with the offer of statin initiation. In some cases, the pharmacist noticed that the patient had moved house but the new address had not been entered onto the practice computer system, meaning the patient would not have received notification of the need for an appointment at the practice if a letter had been sent.

The pharmacist used the time in the practice to collect and summarise eligible patient level information on diagnoses, statin prescribing history and cholesterol levels. Baseline information collected prior to randomisation was used as a starting point for this process. The time spent in the practice also enabled the pharmacist to identify prescribing traits and gaps in care e.g. lack of cholesterol levels which limited the practices' ability to better manage eligible patients. The prescribing traits of individual GPs were recorded whenever possible. In turn, this provided a rich source of information help the pharmacist individualise attempts to improve prescribing. These traits were identified by running searches on the practice computer, or collection of information from handwritten case notes, where it was possible to identify which GP had contact with each patient. In Group practice when these could not be traced to individual GPs, the information was used in summary form during meetings, as a prompt for individual GPs and nurses to reflect on their practices' approach to prescribing. Time spent in the practice and activities were recorded to inform a future economic analysis.

Organisational barriers to increasing the uptake of simvastatin prescribing were noted. These included a lack of willingness in the practice to persevere with invitations for patients who had not attended one or two scheduled appointments. Letters of invitation were sometimes difficult to read, and only offered work-time slots for patients of working age. Updates of patients' phone numbers were often not added to the practice computerised records, which made it difficult to contact patients to arrange appointments. For some housebound patients, who also appeared on the eligible list, practices possibly did not consider visiting at home to deliver an annual check and use the opportunity to start a

statin. In each case, the pharmacist attempted to support the practice in finding ways to engage and implement the key messages of the educational sessions.

3.3.2 Meeting one

Each pharmacist received clear instruction to address the following three objectives during meeting one:

- To enable relationship building between pharmacist and practice staff;
- To evaluate the GP or nurse's awareness and understanding of the HPS trial and statin prescribing guidelines;
- To identify perceived barriers to changing statin prescribing in line with guidance.

Taking approximately 30 minutes, this face to face interactive discussion included a power point presentation, involving the pharmacist and each GP, nurse and other practice staff.

The first meeting helped the GP or nurse to understand the the SOS intervention process and was conducted on a one to one basis in the practice. An open, honest exchange was encouraged. The pharmacist asked some open questions to explore the GP or nurse's usual statin prescribing practice. For example, this may have included asking which statin was prescribed first line, at what point statins were initiated (what was the trigger for initiating a statin), whether patients were assessed for a statin (and other secondary preventive medicines) opportunistically or through planned appointments, was an up to date cholesterol and liver function test result need to be present before statin prescribing. The pharmacist asked about the GP or nurse's awareness and views on the recent Heart Protection Study and recently disseminated statin guideline. The pharmacist took notes during the discussion; in one practice, the pharmacist tape recorded the discussion. All information was retained in the practice, stored alongside patient case notes if paper based or saved onto the practice computer if electronic e.g. power point presentation or summary statistics from baseline.

Having already prepared a summary of the practice's statin prescribing (numbers of patients, statin type, dose, trends over the past few years, cost), this was shared and discussed during the meeting. Other practices' prescribing was used as a comparison. GPs and nurses were asked if they wished to hear the views of 'educationally influential' local opinion leaders and if so, who these opinion leaders were. Sometimes, the GP or nurse had a question about the guideline or HPS or statins, and the pharmacist could not answer it. This prompted a phone call, email or visit to the nominated expert, or to a local consultant. Answers were fed back to the GP/nurse during the second meeting, and if similar questions arose from GPs or nurses in other practices, answers and advice was shared across the network of pharmacists delivering the intervention.

The pharmacist had observed the practice's organisation before meeting one and was encouraged to use these observations and turn them into questions for each nurse and GP during meeting one. In this way, existing prescribing, call and recall procedures were made explicit and discussed openly. This helped to focus the meeting on target setting and consideration of new ways to improve the uptake of guideline based statin prescribing for patients with vascular disease.

Each GP and nurse was asked what they considered to be their own and their practice's key barriers to systematic offering of simvastatin 40mg to each (eligible) patient not prescribed it. If the discussion progressed well, targets were agreed for the desired proportion of

patients with statins and cholesterol controlled, in their practice, at the end of the intervention. Benefits to some GPs were conceptualised in terms of achievement of contract points and therefore remuneration for the practice. To others, the motivating factor was the prospect of offering evidence based prescribing for patients at highest risk. Some GPs and nurses declined to commit to discussions on targets. Instead, they opted to receive the relevant information on their practice's statin prescribing and digest this in their own time before coming to a decision on whether change was necessary or desirable. If this was the case, the pharmacist ensured concise, relevant background information was tailored accordingly. On some occasions, scepticism around the funding of large randomised controlled trials (e.g. belief that the trials are funded by the Pharmaceutical Industry) or questions around the funding for the pharmacist's role prevented the GP from accepting the main messages. Reassurance was developed over time, as the pharmacist was shown to provide added value to the practice, by working steadily, one day per week, carefully identifying patients who could benefit from the intervention, and providing support to the practice to implement change.

Cost savings were projected, in view of the lower cost of simvastatin compared with other statins (one month's supply of generic simvastatin 40mg once daily was £1.32; a commonly prescribed equivalent was Atorvastatin 20mg once daily, costing £26.64 per month).

3.3.3 Between the first and second meetings

Having met with all of the practice's GPs and nurses, the pharmacist had sufficient material to enable preparation of a tailored learning/action plan for each individual GP/nurse and the practice. The pharmacist transcribed the learning and action plan gathered from the one to one meeting with each GP or nurse, into a concise power point presentation (Appendix XII gives an example of a power point presentation from Meeting 2 in a Group Practice). An aggregated version (anonymised) combining all the points asked by all GPs and nurses and provided in response, was prepared for presentation to the practice as a whole. A printed report of the presentation was prepared and circulated after meeting two.

While the content of this report varied between practices, common practical recommendations included the practice (with support from the pharmacist) categorising eligible patients into one of the following groups:

1. Not prescribed a statin
2. Receiving simvastatin but dose suboptimal;
3. Receiving simvastatin 40mg;
4. Prescribed a statin other than simvastatin, optimal dose;
5. Prescribed a statin other than simvastatin, suboptimal dose.

In each case, cholesterol was controlled, uncontrolled or unchecked. This process was time consuming and conducted systematically by the pharmacist, but agreed as necessary by the whole practice, if progress was to be made on the stated objectives.

Appropriate actions were mapped to each category of patient e.g. for those prescribed a suboptimal dose of simvastatin, the pharmacist recommended each patient should receive a letter with a new prescription for simvastatin 40mg, barring contraindications. Based on the pharmacist's impression of the practice's repeat prescribing organisation and the willingness of GPs and nurses interviewed, the pharmacist suggested who should be

responsible for each agreed action. The pharmacist's role in this process was to provide a concise summary of the evidence base and consensus opinion where required. Together with practice staff, the pharmacist screened case notes, noting and recording the category of each patient and updating the practice's disease register. Practices were asked to continue the process of patient identification after the intervention period. In this way, eligible patients included existing and incident patients.

The pharmacist therefore planned appropriate actions and responsibilities for practice staff and matched these to each category of patient. Table 3.1 describes a typical plan.

Table 3.1 Typical actions following a SOS intervention meeting

Category of patient with vascular disease	Intervention by practice team (pharmacist, named nurse, named GP)
Prescribed low potency statin, [§] cholesterol and LFTs known and at target	Switch to simvastatin 40mg by contacting on phone then confirming by letter
Prescribed low potency statin, cholesterol and LFTs not known/not at target	Letter for blood test then switch to simvastatin 40mg
Prescribed potent statin, cholesterol not at target	Phone call to discuss concordance
Prescribed potent statin, cholesterol and LFTs not known/not at target	Letter for blood test then increase dose if necessary
Prescribed potent statin, cholesterol at target	No action
Prescribed low potency statin, cholesterol at target	No action * Check LFTs
No statin; LFTs and Cholesterol known	Letter for appointment for consideration of statin
No statin, LFTs and Cholesterol not known	Letter for appointment for bloods then discussion of need (GP/nurse), leading to Statin prescription
Started on simvastatin 40mg (or other sufficiently potent statin), cholesterol not known	Letter for appointment for bloods

[§] Potency relates to the cholesterol lowering ability of the statin. Low potency statins include Fluvastatin and Pravastatin. Potent statins are all others e.g. simvastatin, Atorvastatin, Rosuvastatin. * Some practices decided, on the weight of the HPS evidence base, to substitute low potency statins with simvastatin.

For each scenario, the pharmacist quantified the number and confirmed the names and contact details (address, phone number) of patients fitting each category. The pharmacist encouraged the practice to agree a follow up date and to name the person responsible for ensuring action. Some patients were excluded from the intervention by the practice.

Typical reasons for exclusion included:

1. Patient known not to wish statin/dose increase;
2. Pregnancy;
3. Change to prescription inappropriate e.g. confused, terminally ill;
4. Patient left practice/died since list produced;
5. Documented intolerance to increased dose or statin.

In practice, simvastatin was commonly prescribed at a suboptimal dose e.g. 10mg. Branded versions were sometimes used; these cost more than generically available alternatives, without conferring any additional benefit. Alternative statins with a less convincing evidence base e.g. fluvastatin, were prescribed. If the practice tended to overuse an

expensive statin e.g. Rosuvastatin instead of simvastatin, the pharmacist clearly articulated the estimated long term impact on prescribing budgets for the practice if the status quo remained. Prior to meeting two, pharmacists found out, from the GP, reasons why Rosuvastatin had been prescribed. All relevant information on Rosuvastatin was obtained and weighed carefully in comparison with the evidence of benefit and costs of simvastatin. The Pharmaceutical Industry representative for Rosuvastatin was contacted by the pharmacist, to ascertain their marketing approach and educational materials, because their detailing often underpinned the GP's statin prescribing decisions.

Workload implications for the practice were considered by the pharmacist in advance of meeting two. Key anticipated actions included time to generate letters to eligible patients, setup a call/recall system, consultation time and time to enter new information onto the practice computer system to ensure long term follow up and sustainability of the changes. The pharmacist anticipated these additional tasks and suggested ways to overcome them. Possible approaches included the practice dividing the list up and allocating part of it to each GP to action, or reception staff agreeing to call patients for an appointment, booked for the GP during any quieter slots. In view of the safety of simvastatin 40mg, some practices agreed to review and/or issue patients with a new prescription by post. The plan was prepared as an interactive, visually appealing presentation on power point, with concise graphic material.

3.3.4 Meeting 2

Practices were asked to protect approximately one hour for this meeting. The pharmacist and all GPs or nurses met together, because consensus building and agreement on next steps required input from all practice staff. If one GP or nurse could not make this meeting, the pharmacist met with them separately to cover the main educational points and practical decisions.

The objective was to gain firm commitment (from all individuals and the entire practice as a unit) on whether, when and how to phase a plan for systematic implementation of the guideline. Having thoroughly considered each part of the implementation plan in terms of workload implications, the pharmacist delivered an interactive presentation including:

- The evidence base;
- A guideline summary;
- Anonymised patient specific prescribing and clinical data;
- Simulation of therapeutic challenges;
- A comparison of the practice's prescribing trends with neighbouring practices;
- Possible targets.

The pharmacist offered the views of respected peers/specialists, having sought and obtained these earlier. A plan for change was described, with timelines; targets (anticipated improvements in prescribing, including tentative quantification of improved clinical outcomes for patients) and lower prescribing costs were discussed. Named GPs and nurses and occasionally other practice staff e.g. Practice Managers were asked to undertake additional tasks to carry the plan to completion. Agreed action always involved the pharmacist committing to ongoing support for creating a register of patients with vascular disease, to complement the practice's efforts. The pharmacist labelled suitable patients' case records, identified barriers to GP or Practice nurse's application of the evidence base in the use of simvastatin 40mg and coached them on ways to overcome these barriers. The pharmacist agreed to steer, monitor and feed back progress on behalf of the practice.

All pharmacists carried a checklist to standardise the content and steer their performance in meeting two, and these points were rehearsed during training:

1. Agree clear educational objectives;
2. Agree clear behavioural objectives;
3. Present both sides of controversial issues;
4. Stimulate active participation;
5. Use concise graphics;
6. Highlight and repeat essential messages;
7. Obtain agreement and build on it;
8. Be enthusiastic;
9. Keep to allotted time.

Meeting two therefore enabled the whole practice to agree on a course of action based on a plan created by the pharmacist, honed through discussion with each GP, nurse and sometimes reception staff or practice manager. Each plan was tailored to the practice's organisation and capacity. It answered questions raised at the first meetings through an interactive presentation, keeping the name of the questioner anonymous if this was necessary (some GPs and nurses chose not to let their colleagues know of gaps in their knowledge although were happy to share this with the pharmacist on a one to one basis).

On some occasions, GPs and nurses were made aware of the evidence base for the first time as a result of meeting two and subsequently agreed to change practice from that point onwards, without the need for further persuasion. However, while the GPs may have changed their first line prescribing to simvastatin 40mg daily, this only applied to incident cases with vascular disease. The bulk of prescribing applied to patients with pre-existing vascular disease; to change the practice's prescribing required modification of prescribing for prevalent cases. If agreement to change prevalent cases was reached during meeting two, the challenge was to involve practice staff in this process.

3.3.5 Between the second and third meetings

Following the meeting, the pharmacist continued to work in the practice on the same day each week. This enabled a continued focus on the implementation of change, reinforcement and provision of feedback through progress reports, until the agreed actions were carried out. Through negotiation, the pharmacist encouraged the practice reception staff, management, GPs and nurses to systematically contact and follow up the agreed list of patients. Agreed actions commonly involved the identification of suitable patients followed by the issue of letters explaining the benefits of statins and requesting the patient's attendance in the practice for a consultation with the practice nurse or GP. The objective of these consultations was to enable the GP/nurse to explain the benefits of simvastatin 40mg to the patient, with a view to the patient agreeing, a new prescription and regular adherence. In some practices, the decision was to identify eligible patients and send a new simvastatin prescription after a telephone call to the patient to explain the change i.e. without the need for a consultation. The pharmacist provided the practice with template letters, relevant to each subgroup of patients. The letters summarised the evidence and explained the benefits. In all cases, the pharmacists' understanding of the practice's capacity and skill mix guided the next steps. The pharmacist did not contact patients directly. Instead, practice staff were encouraged to ask patients to attend opportunistically by phone or letter.

The pharmacist collated feedback, monitored and recorded changes in prescribing. Together these data were summarised and used in the presentation for the third meeting.

3.3.6 Meeting 3

The objectives of meeting three were to:

- Re-iterate key points agreed during meeting two;
- Enable two way feedback, consolidate and reinforce changes to prescribing;
- Address any ongoing implementation difficulties.

It lasted approximately 20 minutes and was conducted face to face, one to one, at a time convenient to the GP or nurse. It enabled feedback on any prescribing changes made in line with the agreement reached during meeting two. This feedback involved comparison of the practice's statin prescribing with targets and estimation of the benefits to patients and cost savings (if any) resulting from the changes. The statin prescribing of other (anonymised) practices over the same time period was used as a comparison. Reinforcement and repetition of key educational messages, reminders of agreed actions and open discussion of progress in relation to timescales were key components of meeting three.

All pharmacists were asked to leave the practice with a firm commitment from the GPs and nurses to continue prescribing simvastatin 40mg for eligible patients.

Key characteristics differentiating the SOS intervention from previous outreach – like interventions include:

- Non academic, non commercialised pharmacists delivering the intervention;
- Access to full patient level clinical and prescribing data;
- Access to, and influence over disease registers and call/recall systems;
- Repeated presence in the practice environment;
- Ability to meet with and influence clinical and non clinical staff;
- Three linked meetings, with sufficient time and opportunity for feedback and reinforcement between meetings;
- The use of several techniques to induce changes in prescribing practice: educational outreach tailored to the needs of the individual practitioner and practice; audit and feedback; reinforcement; reminders; social marketing; educationally influential opinion leaders; and changes to practice administration/ procedures including support for systematic case finding and call / recall;
- A single therapeutic topic combining quality improvement and cost minimisation.

3.4 Usual Care

The SOS intervention was introduced in addition to UC. Practices randomised into UC received no pharmacist-led prescribing support throughout the period of the intervention and did not receive any pharmacist-led prescribing support until at least the end of the follow up period. Usual Care practices were not denied any services and their patients were not denied any treatments. The clinical guideline (Appendix VIII) was posted to all practices in Greater Glasgow. It was based on the HPS. The key recommendation within this guideline was the prescription of simvastatin 40mg for all patients with vascular disease.

3.5 Characteristics of pharmacists and the SOS intervention training programme

Describing the relevant experience of pharmacists and the training given in preparation for the SOS intervention is important for the following reasons:

- Increases the likelihood of reproducibility;
- Enables a better understanding of why the intervention was successful or unsuccessful;
- Demonstrates an important quality control step within the SOS trial planning process.

Eleven prescribing support, practice based pharmacists were selected from 23 employed by NHS GG&C in 2003. The author's role was professional line manager and lead for the Prescribing Support team at that time. Selection of pharmacists to participate was based on availability to deliver the intervention over the year long intervention period. It was not determined by ability or prior knowledge/experience of cardiovascular therapeutics or communication skills. All worked in general practices as prescribing support pharmacists, on a full time or part time basis, all shared the same job description, and were remunerated at the same level under NHS terms and conditions. Key characteristics are given in Table 3.2.

Table 3.2 Pharmacists' characteristics

Pharmacist (Male (M) / Female (F))	Years post qualification	Number of years prescribing support experience*	Role prior to general practice prescribing support	Postgraduate clinical pharmacy qualification	Part time / Full time
#1 (M)	5	4	Community Pharmacy	Y	FT
#2 (F)	2	1	Community Pharmacy	N	FT
#3 (F)	7	4	Community Pharmacy	N	PT (0.6wte)
#4 (F)	7	4	Community Pharmacy	N	FT
#5 (M)	4	1	Community Pharmacy	N	PT (0.2wte)
#6 (F)	5	4	Community Pharmacy	N	PT (0.6wte)
#7 (F)	15	3	Community Pharmacy and Hospital pharmacy (Psychiatry)	Y	PT (0.4wte)
#8 (F)	13	3	Community Pharmacy	N	FT
#9 (F)	6	3	Academia	Y	PT (0.8wte)
#10 (F)	6	3	Community Pharmacy	N	PT (0.6wte)
#11 (F)	12	4	Community Pharmacy	N	FT

* experience was mainly clinical medication review based in general practices, for patients receiving polypharmacy.

To ensure a minimum level of knowledge and skills tailored to the SOS intervention, all pharmacists attended six and a half training days between September 2003 and January 2004. Pre-requisites for delivering the SOS intervention were agreed amongst the pharmacists and included:

- Attendance at all of the study days and achievement of a satisfactory standard (of motivation and performance; assessed by the principle investigator) during each training day;
- Commitment to delivering the SOS intervention in the following 12 months.

Forty one contact hours of training were accrued by each pharmacist. The training was specific to the delivery of the three meeting approach to the SOS intervention. A mixture of academic GPs, GPs experienced in postgraduate education, a consultant cardiologist, a cardiac nurse and a senior lecturer delivered the training sessions. Training covered the following topics:

- Evidence base for use of statins;
- Educational outreach;
- Study protocol;
- Pharmacological actions of statins;
- Aetiology of vascular disease;
- Primary/secondary prevention thresholds;
- Communication skills required to deliver the SOS intervention through three, linked meetings;
- Practitioner and patient level barriers to systematic uptake of simvastatin prescribing;
- Adult learning theory.

An outline of the training provided is given in Appendix XIII. All pharmacists were competent in the operation and searching of practice computer systems. All 11 pharmacists attended the training events and performed satisfactorily.

3.6 Delivery of the SOS intervention

The intervention was delivered as described to 14 of the 16 practices randomised. One practice had disbanded prior to the date of randomisation (this was discovered when the practice was phoned to confirm their allocation) and another practice declined further support, after the first SOS intervention meeting, citing time constraints as the reason. Independent researchers were unable to access this practice for follow up data collection.

With eleven pharmacists available to deliver the intervention, 4 were attached to two practices and the other 7 delivered the SOS intervention to one each. Pharmacists kept to their allocated practices throughout the duration of the study. The pharmacist from the practice that dropped out was retained in the study team and continued to support other participating pharmacists.

3.7 Follow up data collection

Follow up data was collected by hand, from the case notes and/or computer systems of eligible patients in the 29 remaining, participating general practices. Lists of eligible patients were identified using the same computerised search criteria used at baseline. Two trained, independent researchers (blinded to the allocation of practices) visited each practice at least once weekly (dependent on availability of space within each practice) to collect follow up data. The data fields collected by the researchers at follow up are summarised in Table 3.3.

Table 3.3 Data collection fields at follow up

Patient status	Clinical †	Drug	Demographic
Deceased/left the practice	Previous MI	Statin (description of which statin)	Practice identification number
Eligible at baseline (confirmed by date of first eligible diagnosis) or not eligible at baseline (became eligible between baseline and follow up)	Diabetes	Daily dose	Date of data collection
	CABG	Start date	Patient identification number (CHI)
	Stroke,	Dose increase date	Date of birth
	Angioplasty	Most recent cholesterol level	Sex
	TIA	Date of most recent cholesterol level	
	Angina/IHD		
	PVD/Intermittent claudication		

† (eligibility criteria) definite or possible, with accompanying date event(s) first recorded in practice computer

Follow up data collection started on the 4th April 2005 and was completed on 29th March 2006. Across 29 practices, this gave a mean length of follow up of 1.7 years from randomisation (minimum 1.4 years, maximum 2.2 years) as described in Appendix XIV.

Time to first onset of new clinical event/diagnosis

To evaluate the contribution (if any) of the SOS intervention to the development of adverse events, we collected the number and dates of new vascular events in a sample of patients. These data were collected using a remote computer search by a central server (operated by NHS GG&C Information Technology Monitoring Team). In this way, collection of these adverse events was not subject to the same restrictions on access as follow up for endpoints. The mean duration of follow up for events data was 2.5 years (minimum 2.2 years, maximum 2.8 years) (Appendix XIV).

Chapter 4

Baseline data

This chapter describes the characteristics of the SOS study participants at baseline, before randomisation. The characteristics of participating practices are compared with non participating practices and the characteristics of participating patients are compared between the SOS intervention and UC arms of the study. A comparison is made between characteristics of the SOS study participants' and participants of other trials.

4.1 Practice characteristics

As described in the methods chapter, 49 practices were randomly identified from the list of practices in Greater Glasgow at that time and invited to participate. Thirty one practices agreed to participate in the study. The remaining 18 practices either declined to participate ($n = 15$), or did not reply ($n = 3$). Of those agreeing to participate, 15 were Single Handed (SH) and 16 were Group (G) practices. Flow of practices through this stage of the trial is given in Appendix XV.

By the time baseline data collection was complete (this process took 6 months from start to finish) across all 31 practices and practices were randomised, one (single handed) practice had disbanded. The data from this practice is shown in the baseline results for completeness, but is not included after this chapter or used in follow up analysis.

For the 18 practices declining to participate, the number of GPs, practice nurses, list sizes and practice level modified Scottish Index of Multiple Deprivation (mSIMD) was available from routine data. These characteristics were used in comparisons with participating practices. The modified Scottish Index of Multiple Deprivation (mSIMD; McConnachie 2003), is an aggregate score (excluding measures of population health and access to healthcare) indicating the level of socioeconomic deprivation of the practice population. Higher values indicate greater levels of deprivation.

For eligible patients in participating practices, baseline data included the patient level variables described in Chapter 3.

4.1.1 Comparisons between participating and non participating (invited) practices

Characteristics of non participating (invited) practices were compared with the characteristics of participating practices to determine whether those recruited were representative of those invited and by inference, all practices in Greater Glasgow (Table 4.1).

Analyses suggested there were no statistically significant differences in the sizes of practice populations and number of GPs between participating and non participating (invited) practices. The average number of nurses showed a significant difference; participating practices had more (mean 1.2 in participating compared with 0.9 in non participating, $p = 0.04$). When participating and non participating practices' mean values for mSIMD were compared, no statistically significant difference was detectable (38.0 for 31 participating practices, 39.2 for 188 non participating practices; $p = 0.696$).

Table 4.1 Comparisons between participating and non participating (invited) practices

Variable	Participating practices			Non participating (invited) practices			P value
	SH	G	All participating	SH	G	All non participating	
Mean (range)							
Practices	15	16	31	9	8	17	-
GPs	1 (1 - 1)	3.5 (2 - 5)	2.3 (1 - 5)	1 (1 - 1)	3.4 (2 - 6)	2.2 (1 - 6)	0.72 ¹
Practice nurses (PNs)	1 (0.4 - 2)	1.3 (1 - 2)	1.2 (0.4 - 2)	0.72 (0.4 - 1)	1 (0.5 - 1.8)	0.9 (0.4 - 1.8)	0.04 ¹
List size	2043 (818 - 3536)	5374 (1787 - 12330)	3657 (818 - 12330)	1711 (1361 - 2126)	5033 (2584 - 7696)	3323 (1361 - 7696)	0.48 ¹
mSIMD (SD)	36.2 (18.3)	39.8 (10.8)	38.0 (15.5)	42.3 (22.8)	38.0 (20.6)	39.2 (18.9)	0.70 ²

¹Mann-Whitney test²Two sample t-test

4.1.2 Comparisons between the SOS intervention and UC practices

Table 4.2 shows a comparison of the characteristics of participating practices, split by allocation to the SOS intervention and UC. The purpose of the analysis was to test for any differences in SOS intervention and UC practices, in relation to practice level variables at baseline. The number of Whole Time Equivalent GPs, practice nurses, practice list sizes and the eligible patients identified were all comparable between the SOS intervention and UC practices. The aggregated characteristics of SH and G practices within the SOS arm of the study were compared with aggregated characteristics of SH and G practices in the UC arm, using the Wilcoxon signed rank test or the two sample t test.

In the SOS intervention practices, there were 39 GPs and 21 practice nurses. Practices allocated to UC had 32 GPs and 16 practice nurses.

The variable ‘number of whole time equivalent GP or nurse’ was collected to give an indication of the number of meetings required during the SOS intervention, which was anticipated to be a key determinant of whether the SOS intervention would be feasible. Comparison of this variable between the SOS intervention and UC arms using the Wilcoxon Signed Rank test showed them to be well balanced at baseline. Another indicator of the extent of work needed to shift statin prescribing from existing to desirable was the practice list size. This was thought to be proportional to the number of patients eligible; practices with larger lists were thought to pose an increased workload for the practice and pharmacist. Again, SOS intervention and UC practices were found to be balanced in this respect. It might be argued that these variables should have been included in the stratification process, if they were key factors in determining the balance between SOS intervention and UC arms of the study. However, their effect was incorporated indirectly, because stratification involved making a distinction between Single Handed and Group practices, which are defined by the number of whole time equivalent staff (and patients).

Table 4.2 describes a drop off in the number of patients between those labelled ‘eligible identified’ and ‘eligible included’ because of the systematic sampling of every third eligible patient at baseline in the five largest Group practices. Sampling was undertaken because of the limited availability of researchers to undertake the time consuming task of identifying patients from computer records, locating and obtaining paper case notes, finding and documenting relevant information. Three of these practices were subsequently allocated to UC and two were allocated to SOS. Therefore, fewer eligible patients were identified in UC practices than in SOS practices. The Table shows that the number of eligible patients included was modestly imbalanced between SOS intervention and UC, at baseline, as a result of this sampling process. However, the difference did not reach the a priori level of statistical significance (SOS: 296.6 vs. UC: 219.5 eligible patients; $p = 0.09$).

When the practice level mean values for mSIMD were compared between SOS intervention and UC practices, there was no statistically significant difference ($p = 0.3$; 95% CI: -17.1, 5.5). We analysed this variable because those practices with the highest mSIMD are associated with an increased prevalence of CHD and other cardiovascular disorders. In addition, there is some evidence that uptake of general practice appointments for preventative care interventions are reduced among patients from practices with higher mSIMD (The Scottish Government 2008). The extent of social deprivation of recruited practices can also be described relative to the mSIMD of all Scottish practices, to give a broader perspective on practice characteristics. When Scottish practices are divided into deciles according to mSIMD, 10 / 15 SOS arm and 9 / 15 UC practices resided in the two most deprived deciles.

4.1.3 Comparison between Single handed and Group practices

Table 4.2 subdivides practices within SOS and UC arms by their Single Handed and Group practice status. SOS and UC arms of the study were balanced in relation to the given variables.

Overall, these analyses show that, with the exception of practice nurses, participating and invited, non participating practice characteristics were comparable. In the participating practices, practice characteristics were balanced between SOS intervention and UC arms of the study, at baseline, confirming in part, the appropriateness of the randomisation process.

Table 4.2 Baseline characteristics of participating practices

Variable Mean (range)	SOS and UC (Single Handed practices)		SOS and UC (Group practices)		P value SOS (n = 16) vs UC (n = 15)
	SOS (n=8)	UC (n=7)	SOS (n=8)	UC (n=8)	
Whole Time Equivalent GPs	1 (1-1)	1 (1-1)	3.8 (3 - 5)	3.1 (2 - 5)	0.45 ¹
Whole Time Equivalent practice nurses	1.1 (0.4 – 2)	0.9 (0.5 - 1)	1.5 (1 – 2)	1.1 (1 – 2)	0.44 ¹
Practice List size	1967 (818 – 3474)	2119 (1087 – 3536)	5519 (4103 – 7215)	5228 (1787 – 12330)	0.71 ¹
Eligible patients identified	137 (91 - 252)	186 (107 – 275)	545 (426 – 676)	446 (125 – 982)	0.51 ¹
Eligible patients included	66.5 (33 – 133)	89.4 (50 – 135)	230.1 (90 – 296)	130.1 (80 – 237)	0.09 ¹
mSIMD (SD)	34.5 (21.3)	37.8 (15.2)	47.1 (11.8)	32.6 (9.8)	0.30 ²

¹ Wilcoxon signed rank test. ² Two sample t-test.

Table 4.3 shows the numbers of patients in each pair and the triple (from which one practice subsequently disbanded) at randomisation.

Table 4.3 Distribution of eligible, included patients at baseline, by pair

Practice pair	SOS	UC
1	253	155
2	296	100
3 [†]	255	118
4	234	133
5	261	216
6	215	132
7	237	79
8	90	108
9	57	63
10	33	135
11	110	76
12	97	89
13	39	50
14	63	114
15	133	99
Sub total	2373	1667
Total	4040	

[†] Triple, containing 2 (Single Handed) SOS arm practices

4.2 Patient characteristics

4.2.1 SOS versus UC

Baseline data collection included demographic, diagnostic and prescribing data from the computer and paper records of 4040 patients across 31 practices.

Table 4.4 shows SOS and UC practices were well matched for mean age and sex of the patients recruited. Both variables were comparable to population estimates for patients with Coronary Heart Disease at that time (Allender 2007).

The most prevalent qualifying diagnosis was Angina/Ischaemic Heart Disease (IHD) with a statistically significant higher prevalence in the SOS arm (49.3% versus 40.4%, $p < 0.001$). The prevalence of all other diagnoses was balanced between SOS and UC practices at baseline.

The co-morbidities collected during the study related only to those described in the HPS for patient inclusion criteria. The prevalence of vascular co-morbidities was significantly higher in SOS than in the UC arm, but the difference was nullified when adjusted for the contribution of Angina/IHD. There was no evidence of difference in the prevalence of any other diagnoses, indicating that practices randomised to the SOS intervention were broadly comparable to practices randomised to UC in relation to distribution of qualifying diagnoses.

Table 4.4 Patient characteristics at baseline (SOS vs. UC): demographics and co-morbidities

	SOS (n = 2373 with vascular disease)	UC (n = 1667 with vascular disease)	p value
Age (years) †	68.2 (12.1)	68.5 (12.0)	0.31 ¹
Sex, male	1207/2373 (52.9%)	890/1667 (53.4%)	0.19 ²
Qualifying diagnosis			
Values shown are number (%) of patients with each type of vascular disease			
Angina / Ischaemic Heart Disease	1170/2373 (49.3%)	674/1667 (40.4%)	< 0.001 ²
Diabetes Mellitus, age ≥ 45 years	825/2373 (34.8%)	647/1667 (38.8%)	0.34 ²
MI	495/2373 (20.8%)	355 /1667 (21.2%)	0.33 ²
Cerebrovascular event	334/2373 (14.1%)	236/1667 (14.1%)	0.11 ²
PVD	286/2373 (12.0%)	161/1667 (9.6%)	0.20 ²
TIA	223/2373 (9.4%)	121/1667 (7.2%)	0.16 ²
CABG	200/2373 (8.4%)	144/1667 (8.6%)	0.54 ²
Angioplasty	104/2373 (4.4%)	67/1667 (4.0%)	0.67 ²
Number of vascular co-morbidities †	1.53 (0.78)	1.44 (0.72)	< 0.001 ¹
Number of vascular co-morbidities excepting angina †	0.81 (0.72)	0.84 (0.66)	0.76 ¹

¹ Linear regression ² Binary logistic regression † Mean (SD)

Table 4.5 shows cholesterol levels of patients in the SOS intervention and UC arms of the study. Approximately one quarter of patients in the SOS arm had no record of their cholesterol ever being recorded in their primary care medical case records. The proportion of UC patients without cholesterol ever recorded was less (21.6% UC vs 25.4% SOS, $p = 0.01$).

Of those with cholesterol recorded, approximately half of all participants had cholesterol levels below target (threshold < 5mmol/l for all patients except those with a diagnosis of CABG, who had a target of < 4mmol/l). The values shown in Table 4.5 (49.7% SOS and 52.0% UC) included all patients (with or without a statin) at baseline.

Of those with cholesterol recorded, mean cholesterol levels for patients prescribed a statin (4.79mmol/l SOS, 4.71mmol/l UC) were (as expected) lower than in patients without a statin (5.11mmol/l SOS, 5.08mmol/l UC). Neither of these variables showed any evidence of difference when SOS practices were compared with UC. There were significant differences between the SOS intervention and UC in the prescribing of statins (38.6% SOS, 44.3% UC; $p < 0.001$) and in the prescribing of statins at optimal doses (21.9% SOS, 24.5% UC; $p < 0.001$) when all patients (with or without a statin) were included.

Stratification comprised matching of practices according to the variable thought to be the most important predictor of effect:

$$\frac{\text{Number of eligible patients with cholesterol recorded and in target range}}{\text{Number of eligible patients}}$$

This variable was balanced at baseline (49.7% SOS vs. 52.0% UC; $p = 0.48$) but other variables e.g. statin prescribed or prescribed at optimal dose, were not.

Table 4.5 Patient characteristics at baseline (SOS vs. UC): cholesterol levels and statin prescribing

	SOS (n = 2373 with vascular disease)	UC (n = 1667 with vascular disease)	p value
Statin prescribing and cholesterol			
Cholesterol recorded	1768/2373 (74.5%)	1307/1667 (78.4 %)	0.01 ²
Cholesterol recorded and controlled	878/1768 (49.7%)	680/1307 (52.0%)	0.48 ²
Mean Cholesterol level , all patients with cholesterol level (SD)	5.08mmol/l (1.1mmol/l)	5.01mmol/l (1.1mmol/l)	0.14 ¹
Mean cholesterol level, all patients with cholesterol recorded and prescribed a statin (SD)	4.79mmol/l (1.2mmol/l)	4.71mmol/l (1.1mmol/l)	0.20 ¹
Mean cholesterol level, all patients with cholesterol recorded and not prescribed a statin (SD)	5.11mmol/l (1.1mmol/l)	5.08mmol/l (1.0mmol/l)	0.82 ¹
Statin not prescribed	1456/2373 (61.4%)	929/1667 (55.7%)	< 0.001 ²
Statin prescribed at optimal dose	520/2373 (21.9%)	408/1667 (24.5%)	< 0.001 ²

¹Linear regression

²Binary logistic regression

Table 4.6 characterises all 1654 patients with vascular disease who were prescribed a statin at baseline. For patients with vascular disease prescribed a statin, there was no significant difference between SOS and UC arms in the proportion with cholesterol not recorded in medical case notes (assumed therefore that cholesterol has never been checked; 9.8% SOS vs. 8.8% UC; $p = 0.61$) and no difference in the proportion with cholesterol controlled (50.3% SOS vs. 51.2% UC; $p = 0.93$).

For each statin and within each of the statin subcategories, there appeared not to be any significant imbalance between patients in the SOS intervention and UC arms of the study. For each of the statins (Simvastatin, Atorvastatin, Pravastatin and Fluvastatin) shown in Table 4.6, the SOS intervention and UC arms were balanced at baseline. Together, this indicates the randomization process achieved the desired effect and that any difference in this outcome at follow up could be attributed to the intervention effect.

Simvastatin was the most prescribed statin at baseline, with almost double the proportion of patients than the nearest competitor, Atorvastatin. When patients prescribed a statin at baseline were considered, the only (weak) evidence of there being any difference in the

distribution of statin prescribing between SOS and UC practices was a slightly greater proportion of patients in the UC arm prescribed Atorvastatin (29.4% UC vs 27.7% SOS; $p = 0.04$). Only 63% of the simvastatin treated group were prescribed an evidence based dose compared with 100% in the Atorvastatin group. This is likely to be due to the starting dose of Atorvastatin (10mg) being accepted as a maintenance dose, due to it having greater potency. In contrast, simvastatin is commonly initiated at 10mg or 20mg with the requirement for the patient to re-attend their practice for up titration to 40mg (the optimal dose). This may take several weeks or months. The requirement for additional appointments can lead to dropout with those dropping out more likely to stabilise at a lower dose.

Table 4.6 Patient characteristics at baseline (SOS vs. UC): statin prescribing

Variable		SOS (n = 916 prescribed a statin)	UC (n = 738 prescribed a statin)	p value
Cholesterol not recorded		90/916 (9.8%)	65/738 (8.8%)	0.61 ²
Cholesterol recorded and controlled		461/916 (50.3%)	378/738 (51.2%)	0.93 ²
Simvastatin	All doses	529/916 (57.8%)	443/738 (60.0%)	0.15 ²
	Suboptimal dose	318/916 (34.7%)	286/738 (38.8%)	0.89 ²
	Optimal dose, cholesterol controlled	91/916 (9.9%)	72/738 (9.8%)	0.43 ²
	All doses, cholesterol controlled	259/916 (28.3%)	226/738 (30.6%)	0.31 ²
	Mean Cholesterol level (SD)	4.77mmol/l (1.15mmol/l)	4.70mmol/l (1.13mmol/l)	0.21 ¹
Atorvastatin	All doses	254/916 (27.7%)	217/738 (29.4%)	0.04 ²
	All doses, cholesterol controlled	143/916 (15.6%)	120/738 (16.3%)	0.47 ²
	Mean cholesterol level (SD)	4.75mmol/l (1.20mmol/l)	4.66mmol/l (1.14mmol/l)	0.69 ¹
Pravastatin	All doses	119/916 (7.7%)	70/738 (9.5%)	0.18 ²
	Suboptimal dose	70/916 (7.6%)	37/738 (5.0%)	0.89 ²
	Optimal dose, cholesterol controlled	20/916 (2.2%)	17/738 (2.3%)	0.56 ²
	All doses, cholesterol controlled	55/916(6.0%)	28/738 (3.8%)	0.32 ²
	Mean Cholesterol level (SD)	4.98mmol/l (0.97mmol/l)	4.95mmol/l (1.15mmol/l)	0.93 ¹
Other statins	All doses	14/916 (1.5%)	8 (1.2%)	-

¹Linear regression²Binary logistic regression

4.2.2 Single Handed vs. Group

Table 4.7 describes key patient variables by SH and G practice status. These data confirm there to be some important differences, therefore justifying the decision to stratify. Patients were on average, three years younger in SH practices, but the difference did not reach statistical significance. There were significant differences in the prevalence of PVD, Stroke and TIA. The prevalence of all of these diagnoses was lower in SH practices.

Table 4.7 Patient characteristics (G vs. SH practices): demographics and vascular co-morbidities

Variable	Group (n = 16 practices; 2,882 patients)	Single Handed (n = 15 practices; 1,158 patients)	p value
Mean age, years (SD)	68.6 (12.0)	65.8 (12.0)	0.04 ¹
Sex, male (%)	51.7%	53.6%	0.10 ²
General Practice mSIMD (SD)	39.8 (12.9)	36.0 (18.1)	0.51 ¹
Qualifying diagnosis (median % prevalence, range) ¹			
MI	21.0 (12.4 – 27.2)	19.3 (6.7 – 35.9)	0.36
CABG	8.3 (4.6 – 16.5)	8.0 (0 – 15.1)	0.87
Angioplasty	3.8 (1.2 – 8.2)	5.2 (0 – 11.1)	0.43
Angina / Ischaemic Heart Disease	45.8 (23.7 – 64.7)	45.1 (10.4 – 59.6)	0.25
PVD	12.5 (8.7 – 20.7)	7.1 (0 – 23.8)	0.003
Diabetes Mellitus, age ≥ 45 years	32.5 (17.1 – 43.7)	35.3 (26.9 – 91.8)	0.05
Cerebrovascular event	16.6 (9.0 – 23.7)	7.5 (1.5 – 23.7)	0.009
TIA	10.1 (2.5 – 12.7)	5.3 (0 – 15.5)	0.05
Mean number of patients with more than 1 co-morbidity [†]	0.52 (0.77)	0.44 (0.73)	0.16

¹Two sample t-test. ²Kruskal Wallis test † Mean ± SD

Table 4.8 shows that there was no evidence of a significant difference between G and SH practices in relation to statin prescribing or cholesterol variables. Amongst those prescribed simvastatin, fewer patients in SH practices were on the optimum dose and had their cholesterol controlled (one of the secondary outcome measures), justifying stratification of this variable (median proportion across Group practices 45.0%; range 16.7 to 72.2% vs 25.0%; range 0.0 to 76.2% across SH practices; p = 0.001).

The only other characteristic shown to be significantly different was the median proportion of patients receiving an optimal dose of statin with controlled cholesterol. However, the statistical power of the analyses comparing SH with G practices (Kruskal Wallis test of aggregated data; no need to take account of pairing in this analysis) was much reduced compared with the analysis of SOS versus UC (binary logistic regression of individual data).

Table 4.8 Patient characteristics (G vs. SH practices): statin prescribing

Variable	Group (n = 16 practices; 2,882 patients)	Single Handed (n = 15 practices; 1,158 patients)	p value¹
All participants: statin prescribing and cholesterol: median % (range)			
Cholesterol recorded	77.3% (51.3 – 94.4%)	84.6% (59.6 – 98.1)	0.09
Cholesterol recorded and controlled	50.9% (30.7 – 67.6%)	52.1% (28.6 – 73.9)	0.50
Statin not prescribed	58.7% (32.3 – 78.0%)	58.6% (38.0 – 96.8%)	0.86
Statin prescribed at optimal dose	53.2% (32.8 – 88.3%)	56.7% (0.0 – 62.7%)	0.87
Mean Cholesterol level (SD)	4.95mmol/l (1.13)	4.92mmol/l (1.07)	0.81 ²
Participants prescribed any statin			
Mean cholesterol level (SD)	4.78mmol/l (1.14)	4.77mmol/l (1.13)	0.90
Participants prescribed simvastatin			
All doses	59.4% (41.7 – 78.3%)	53.8% (27.3 – 100%)	0.39
Suboptimal dose	66.1% (28.0 – 77.4%)	71.4% (34.4 – 100%)	0.10
Optimal dose, cholesterol controlled	45.0% (16.7 – 72.2%)	25.0% (0.0 – 76.2%)	0.001
All doses, cholesterol controlled	51.2% (28.3 – 72.1%)	45.8% (16.7 – 100%)	0.45
Mean Cholesterol level (SD)	4.72mmol/l (1.14)	4.80mmol/l (1.14)	0.49
Participants prescribed Atorvastatin			
All doses	23.8% (9.1 – 56.7%)	24.1% (0.0 – 63.6%)	0.86
All doses, cholesterol controlled	52.8% (0.0 – 82.4%)	59.6% (0.0 – 84.6%)	0.59
Mean cholesterol level (SD)	4.81mmol/l (1.19)	4.76mmol/l (1.13)	0.6
Participants prescribed Pravastatin			
All doses	8.8% (0.0 – 29.5%)	10.6% (0.0 – 40.0%)	0.77
Suboptimal dose	50.0 (0.0 – 92.9%)	41.7% (0.0 – 100%)	0.74
Optimal dose, cholesterol controlled	37.5% (0.0 – 100%)	83.3% (0.0 – 100%)	0.24
All doses, cholesterol controlled	25.0% (0.0 – 100%)	64.6% (0.0 – 100%)	0.09
Mean Cholesterol level (SD)	5.04mmol/l (1.06)	4.73mmol/l (0.95)	0.23
Other statins e.g. Fluvastatin			
All doses	0.0% (0.0 – 3.3%)	0.0% (0.0 – 19.0%)	-

¹Kruskal Wallis test ²Two sample t test

4.3 Discussion of baseline data

4.3.1 Practice characteristics

Our 50:50 ratio of Group to Single Handed practices did not mirror the 70:30 ratio in Glasgow at the time of recruitment, therefore we compared key characteristics of our participating practices with invited, non participating practices as a way of demonstrating representativeness. Baseline data suggested the recruited sample of 15 Group and 16 Single Handed practices was comparable to the 24 Group and 25 Single Handed practices invited to participate, although the number of practice nurses was slightly greater in participating practices. As the process for selection of these 49 practices from the Glasgow list of 169 Group and 63 Single Handed was random, recruited Group and Single Handed practices are otherwise likely to be representative of those in the largest Health Board in Scotland.

While the greater number of practice nurses in participating practices reached statistical significance, it is not possible to speculate if the difference (0.3 whole time equivalent practice nurse between participating and invited, non participating practices) influenced the practice's decision to participate in the study. If practices with fewer practice nurses can be assumed to be busier as a result, those with fewer may have declined to participate because of a perceived inability to accommodate the intensive schedule of meetings and pharmacist input. Alternatively, invited, non participating practices may not have viewed the topic of improving secondary prevention by statin prescribing as a priority. Both these potential reasons might suggest lower levels of achievement of the variables described, in non participating practices.

Characteristics of practices allocated to SOS intervention showed no statistically significant differences compared to practices allocated to UC. Only one comparison generated a difference that approached statistical significance: the number of patients eligible for inclusion in the target group for pharmacist intervention. In UC, Group practices, the mean number of eligible patients identified by the researchers was almost half the number in the SOS arm (Group practices): 130.1 vs. 230.1. This difference was likely to have accounted for the difference between the SOS intervention and UC nearing statistical significance ($p = 0.09$; Table 4.2). The reasons for this imbalance did not appear to come from differences in the practice list sizes used to derive them, because these were comparable ($p = 0.71$; Table 4.2). It is likely that the sampling process (every third eligible patient in the five largest Group practices) led to the identification of fewer patients in the UC arm practices. As practices had not been allocated to UC or the SOS intervention at the time of baseline data collection, this imbalance occurred as a result of a greater number (three) of these practices being allocated to the UC arm and two to the SOS arm. Allocation to SOS or UC was by a computer generated list of random numbers. It is unlikely to have confounded the results, because the lower number of patients identified did not account for any subsequent differences in any of the characteristics described in Tables 4.4 to 4.8 the numerator was expressed as a percentage of the number of patients sampled.

Comparison of our recruited general practices' characteristics with other studies is not possible because practice level characteristics are inadequately described in other studies of this nature.

4.3.2 Patient characteristics

At baseline, only 41% of eligible patients were prescribed a statin, and just over half of these were prescribed a statin at an evidence based dose (Table 4.5). At best, 59% of those on a statin had controlled cholesterol, a finding consistent with the ‘rule of halves’ (Wilber 1972). Although the findings were not aligned to the rule of halves, Primatesta found cholesterol targets were achieved in less than 50% of patients who receive lipid lowering treatment (Primatesta 2000). Other researchers have found a similar picture, in relation to LDL cholesterol levels (Bourgault 2005; Farahani 2009). These data indicate the potential importance of an intervention to improve statin prescribing and cholesterol levels, in primary care.

There was a higher prevalence of angina/IHD in the SOS intervention arm (49.3% versus 40.4%, $p < 0.001$. Table 4.4). Greater numbers of patients with angina/IHD may indicate the practice had improved approaches to detecting and recording angina/IHD, or higher baseline prevalence compared to practices with fewer numbers. Either way, a greater amount of effort is required to establish and maintain accurate disease registers if there are more patients. Associated with this is the need to manage call and recall systems for annual cholesterol, blood pressure and other checks, all of which increase workload in general practices (Moher 2001). It is therefore possible that the SOS intervention allocated practices were more accustomed to managing disease registers with larger numbers of patients with CHD compared with UC practices, and this prepared them better for additional work arising from the SOS intervention. The increased prevalence of angina/IHD caused the statistically significant difference in the number of vascular co-morbidities, with a greater proportion in the SOS arm compared with the UC arm (SOS: 1.53 (SD 0.78) vs. UC: 1.44 (SD 0.72). p -value < 0.001 . Table 4.4). Baseline data collected in each practice was available to each practice prior to randomisation.

Statin prescribing and optimum dosing was less in the SOS intervention arm, when all eligible patients ($n = 2373$, with or without a statin) in SOS intervention arm were compared with all eligible patients in the UC arm ($n = 1667$; Table 4.5). One reason for these imbalances could be the relatively small number of clusters, and large variation between clusters. Analysis of follow up data did not adjust for these baseline differences; only practice type (SH or G) and pairing were adjusted for in the regression analysis. However, these imbalances tended to work against the effect of the SOS intervention, rather than introduce bias to favour the SOS intervention.

From Table 4.6, the proportion of patients receiving simvastatin with their cholesterol controlled was almost double the proportion controlled on Atorvastatin, a surprising finding in view of the greater potency of Atorvastatin and relative ease of attainment of the target dose. However, mean cholesterol levels were comparable in patients prescribed both statins. The explanation for this finding is uncertain, but local Guidelines (Appendix VIII), recommended Atorvastatin as second line, after attempts to bring cholesterol under control with simvastatin have failed. Therefore, patients commenced on Atorvastatin may be more likely to have higher cholesterol levels at the outset, or cholesterol levels less likely to show a decrease (for whatever reason e.g. poor adherence).

Pravastatin is known to be less potent (mg for mg) than either simvastatin or Atorvastatin, which explains why patients receiving Pravastatin had higher cholesterol levels than patients prescribed simvastatin or Atorvastatin.

As expected, mean cholesterol levels at baseline for patients prescribed a statin (4.71mmol/l UC, 4.8mmol/l SOS; Table 4.5) were lower than mean cholesterol levels for

patients without a statin (5.11mmol/l SOS, 5.08mmol/l UC), an approximate reduction of 7%. This reduction is of a lower magnitude to that observed in landmark statin intervention trials where reductions in cholesterol were of the order of approximately 27% (Scandinavian Simvastatin Survival Study Group 1994; Sacks 1996; The LIPID study group 1998; Shepherd 1995; Downs 1998; The Heart Protection Study Collaborative Group 2002; Shepherd 2002; ALLHAT Collaborative research group 2002; ASCOT investigators 2003; Serruys 1999; Schwartz 2002; Athyros 2002) and differences in morbidity/mortality outcomes emerged over a minimum of 3 years. Possible reasons for the reduced effect of statins in our naturalistic study might include the use of lower than optimal doses, reduced statin adherence, recent initiation with insufficient time for maximal cholesterol lowering effect, and a more unpredictable impact in a heterogeneous group of primary care based patients not usually included in clinical trials. Patients consenting to participate in commercially driven, multicentre clinical trials may be more likely to be 'health wary': in providing signed consent to participate, they have agreed to a schedule of additional clinic visits and taking an additional tablet every day. In comparison, the SOS intervention trial participants were operating as they do in usual care, because Ethical approval did not stipulate the need for patient consent. Unlike participants in landmark statin trials, patients in the SOS intervention target group did not receive the additional attention from dedicated research staff for follow up blood tests, repeat medicine supplies and encouragement to adhere. Reinforcement through repeat visits to study centres in other trials may have the effect of improving adherence (Mullen 1985) and therefore reduced cholesterol to a greater extent.

We hypothesised there would be significant differences between SH and G practices at baseline, and stratified for this reason. Although unsubstantiated by any empirical evidence collected during the study, pharmacists observed that group practices tended to have more advanced protocols for case finding, call and recall and more complete computerised data recording than single handed practices. All of these attributes might be expected to lead to increased detection and recording. Diabetes was the exception to this observation with an increased prevalence in single handed practices compared with group practices. This could be explained by the fact that four single handed practices were located in predominantly South Asian communities. South Asians are up to six times more likely to get diabetes, develop it on average 10 years earlier (Mather 1985; Greenhalgh 2001) and have a 50 per cent increased mortality risk from coronary heart disease compared with white Europeans (Wild 1997). The proportion of patients with vascular disease who had diabetes across these four single handed practices was 81.1% compared with 36.3% across the remaining 11 recruited single handed practices.

In 1995, for a primary prevention cohort of patients in the WOSCOPS (some of whom were from the practices recruited into the SOS intervention trial), mean cholesterol at baseline among screenees was 5.9 ± 1.2 mmol/l (Shepherd 1995). The mean cholesterol level among patients at baseline in the SOS trial, 10 years after WOSCOPS baseline, was lower. This was an expected finding because approximately 40% of our participants were already receiving a statin. In addition, at baseline (2003/4), there was greater societal and individual level awareness of the need to reduce cholesterol, compared with 1995, when cholesterol and statins were emerging as important factors in the management of CHD. However, our results demonstrate that important shortfalls in cholesterol control and statin use persisted in a higher risk, secondary prevention cohort: approximately half of patients had no statin prescription and had cholesterol above target. Other reports from around the same period indicated that only 1 in 10 eligible patients reached recommended targets (Primatesta 2000).

In 2002, a survey of British men with established CHD aged 60 – 75 years showed up to 33% were prescribed a statin with only a third of those prescribed a trial validated dose (Whincup 2002). We report the results from a larger sample from the same period, with comparable results (approximately 40% prescribed a statin, half of those prescribed trial target dose) confirming the generalisability of our baseline findings. Simvastatin was the most prescribed, accounting for 59% of all statins and double the number of patients compared with the nearest competitor, Atorvastatin.

We systematically collected few demographic variables other than age and gender, because of the limitations of time and the extent of missing data for other variables e.g. smoking status, blood pressure. Cholesterol levels were available in 81% of participants; we did not conduct any physical examination of the eligible patients in the study practices.

Comparison of the characteristics of the SOS study participants with participants in published trials enables an evaluation of generalisability and an understanding of whether the study adds to current knowledge or understanding in this area. There are two types of study suitable for comparison with the SOS trial: landmark randomised controlled trials of statin therapy for secondary prevention and surveys of statin prescribing (Tables 4.9 and 4.10).

4.3.3 Characteristics of SOS trial participants compared with placebo controlled secondary prevention statin trials

The SOS study population appears broadly comparable with those included in landmark secondary prevention studies. Demographics, physiological measures and co-morbidities are compared with other statin trials from that period in Table 4.9. Most parameters are similar, with two notable exceptions: the SOS trial had higher prevalence of Angina/IHD and Diabetes. This is likely to be a reflection of the underlying high prevalence known in the Greater Glasgow population (Figure 3.1).

While acknowledging differences in funding, aims, multicentre location and methodology, the SOS trial participants are comparable with the PROSPER study (Prosper study group 2002). PROSPER was a randomised controlled trial involving 5804 elderly people with or at high risk of developing cardiovascular disease or stroke. Patients were recruited from Glasgow, Cork and the Netherlands in 1998/9. The intervention comprised Pravastatin 40mg daily for 3 years with a mean follow up of 3.2 years. While the follow up period was shorter in the SOS study and participants were younger, most other parameters were similar e.g. prevalence of stroke, peripheral vascular disease, CABG and angioplasty (Table 4.9). The proportion of males in SOS was 53% compared with 48% in PROSPER. PROSPER achieved a statistically significant reduction in the primary endpoint of a composite of coronary death, non fatal myocardial infarction or stroke. The difference between intervention and control group in the number of patients receiving Pravastatin 40mg was 2900.

In view of the similarities in the risk profiles of the participants in the SOS study and PROSPER, the SOS intervention participants receiving simvastatin 40mg may have achieved comparable endpoints, if there was sufficient difference between the SOS intervention arm and UC arm statin prescribing and the follow up period was longer. Chapter 6 discusses the scale of the changes in the SOS study and potential clinical significance of these.

HPS and LIPID (LIPID study group 1998; Table 4.9) recruited larger numbers of patients than those participating in the SOS trial. All three including CARE (Sacks 1996) recruited predominantly male, younger patients and followed outcomes for longer. Acknowledging the fundamental differences between the SOS intervention and these trials e.g. placebo controlled vs. comparative effectiveness, formal selection, recruitment and randomisation of patients vs. practices, a particularly novel aspect of the SOS trial is the involvement of a high proportion of diabetic participants.

HPS had an age limit of 80 years at inclusion; therefore, the SOS participants were older on average (61% of participants over 65 years compared to 46% in HPS). The proportion of male versus female also differed: HPS (in common with all other landmark statin trials except PROSPER), recruited predominantly male participants. The SOS study included approximately equal numbers of males and females, suggesting better representativeness to usual care. Other baseline characteristics were comparable (e.g. prevalence of CHD, Stroke/TIA, PVD, Diabetes) between studies. The HPS investigators targeted patient groups who had been previously underrepresented or in whom the evidence of statin use needed to be reinforced (Chapter 3: methods). Patients entered into the trial were further selected on their ability to take their simvastatin. In the SOS study, pragmatic criteria were used to identify suitable patients on the basis of having at least one vascular co-morbidity. Disease prevalence also differed between the SOS intervention and HPS; the older age group in SOS had, as expected, a higher prevalence of CHD/ angina.

Table 4.9 shows cholesterol levels (in statin – naïve individuals at baseline in all studies) were lower in the SOS trial. The reasons for this are not obvious, but in SOS trial we were only able to collect cholesterol levels if these were recorded in medical case records. Twenty four percent of eligible patients had no record of cholesterol levels: these patients are likely to have received an invitation for a cholesterol check at some point in the past, but did not attend. If this non attendance is taken as a signal of reduced health seeking behaviour or ‘health wary’ attitude, cholesterol levels may have been higher in patients without a record of cholesterol level. The mean cholesterol may have increased if the missing 24% had their cholesterol levels checked.

4.3.4 Characteristics of SOS trial participants compared with secondary prevention surveys

Statin prescribing and cholesterol levels in comparison with secondary prevention surveys from that period are compared in Table 4.10. It is acknowledged that different settings bring differences in lifestyle, healthcare systems and prescribing trends, all of which may impact on statin prescribing and cholesterol level.

The SOS trial provides data from two time periods: baseline (2003/4) and follow up (2005/6). EUROASPIRE (2001) and PREVESE (De Velasco 2002) also collected statin prescribing and cholesterol levels from the same locations at two different time periods. However, only EUROASPIRE data is shown in Table 4.10. EUROASPIRE (2001) and ASPIRE (ASPIRE steering group 1996) recruited patients post discharge from hospital following a coronary event. ASPIRE was a cross sectional survey of a representative sample of coronary patients from a (retrospective) review of hospital medical records.

The relatively high proportion of patients with cholesterol above the threshold in ASPIRE (86%) was comparable with the EUROASPIRE I (EUROASPIRE I and II group 2001) and L-TAP (Pearson 2000) surveys from the same period (1994 – 7). In 1996, when ASPIRE was published, the British Hyperlipidaemia Society’s guidelines were available and

passively disseminated, but these stressed the importance of first introducing dietary measures to reduce cholesterol and only if this approach failed, a statin prescription was recommended (Betteridge 1993). In practice, this guidance may have limited the prescribing of statins because some patients might have dropped out of follow up at the dietary modification stage, thus reducing numbers presenting for a statin.

Nevertheless, CARE, LIPID and WOSCOPS had all been published at that point, and had clearly justified the prescribing of statins without the need for previous failed attempts at dietary modification. ASPIRE results from 3 years previously showed considerable scope for improvement in statin prescribing, when compared with reports from Europe and North American populations.

A gradual reduction in cholesterol over time was noted by Evans in 2001 and this trend was confirmed in EUROASPIRE II (Table 4.10: 59% above target). The SOS study baseline results were collected three years after EUROASPIRE II and showed that only a marginally increased proportion of patients (61%) were above target. During this three year intervening period, five additional landmark trials had been published, consolidating and reinforcing the already strong evidence base for statin use: PROSPER, MIRACL (Schwartz 2002), GREACE (Athysos 2002), FLARE (Serruys 1999), and AFCAPS (Downs 1998). In addition, meta analyses had confirmed beyond reasonable doubt that reductions in cholesterol and LDL-cholesterol associated with statins caused a decrease in the risk of heart disease and all cause mortality (Law 2003; La Rosa 1999).

Together, the widespread publication of additional evidence between EUROASPIRE I and II and the lack of progress with achievement of target cholesterol levels reinforces the weak effect of passive dissemination if the aim is to change prescribing practice.

The North American L-TAP survey determined the percentage of patients with confirmed hyperlipidaemia who had reached cholesterol targets (Pearson 2000). One thousand, four hundred and sixty patients with established CHD were included, and only 18% were found to have achieved (LDL) cholesterol targets. Possible explanations included the low uptake of statin prescribing, use of sub-optimal doses (proportions were not described in the paper) and poor compliance among patients. Recommendations from this survey included more widespread prescribing of statins, and prescribing of higher doses.

Other surveys have been conducted which reinforce the generalisability of SOS data shown in Table 4.10, but due to an insufficient description of the patient characteristics or prescribing, lack sufficient detail to enable comparison (Baxter 1998; Schrott 1997). It is notable that Baxter highlighted the issue of variation between practices, finding that almost 100 – fold variation existed during the period 1990 – 96, for prescribing of lipid lowering agents, within the South East Thames region. This was despite attempts to improve prescribing through dissemination of local cholesterol and statin prescribing guidance, again underscoring the need for some means of improving prescribing and reducing variation.

Table 4.9 Baseline characteristics of patients in the SOS study and landmark secondary prevention statin trials

	SOS	PROSPER	CARE	LIPID	HPS
	Vascular disease	Vascular disease / multiple risk factors	MI	CHD	Vascular disease
n =	4,040	5,804	4,159	9,014	20,536
Mean follow up (years)	1.7	3.2	5	6.1	5
Patient characteristics					
Age (yr)	68	75	59	62	40 – 80 ^x
Sex (male) %	53	48	86	83	75
<i>Physiological measures</i>					
Mean Cholesterol (mmol/l)*	5.1	5.7	4.5 [§]	5.8	5.9
<i>Co-morbidities (%)</i>					
Angina/IHD	46	27	21	36	24
MI	21	13	100	64	41
Stroke	14	9	-	4	16 [†]
TIA	9	17	-	4	-
PVD	11	9	-	10	33
Diabetes	36	11	14	9	29
CABG	9	6	27	27	-
Angioplasty	4	4	34	11	-

† combined with TIA

‡ combined with angioplasty

§ entry criteria < 4.5mmol/l * statin free ^x46% > 65

Table 4.10 Statin prescribing at baseline in the SOS study and other statin surveys

	SOS (2003/4)	EUROASPIRE I (1995/6)	EUROASPIRE II (1999/00)	ASPIRE (1994/5)	L –TAP (1996/7)
n	4040	3569	3379	2583	4888
Location	Scotland	Europe (excluding UK)	Europe (excluding UK)	UK	North America
Patient characteristics	MI, CHD, Angioplasty, CABG, Diabetes, PVD, Stroke, TIA	MI, CHD, Angioplasty or CABG	MI, CHD, Angioplasty or CABG	MI, CHD, Angioplasty or CABG	Hyperlipidaemic [§]
Cholesterol with statin	4.75	-	-	-	-
Cholesterol without statin	5.10	-	-	-	-
<u>Cholesterol above target range (%)</u> [§]	61	86	59	78	82
<u>Any lipid lowering (%)</u>	41	32	63	10	27
<u>Any statin (%)</u>	41	19	58	-	21
<u>Any statin, any dose, controlled cholesterol (%)</u>	21	21	49	< 5	39

[§]Data shown for CHD participants only

Chapter 5

Follow up results

This chapter presents the results of the SOS trial. These include the primary and secondary outcomes with subgroup analyses and exploratory analyses of adverse effects (restricted to a sample of patients with vascular events).

In most studies, data is collected at follow up for as many of the patients identified at baseline, as possible. The SOS study was naturalistic, and, unusually, at follow up, in addition to collecting data for patients identified at baseline, the opportunity arose to collect relevant data for patients who became eligible (through first recording of a vascular diagnoses) between baseline and follow up. This created the opportunity to assess the treatment effect on incident (first recording of vascular diagnosis between baseline and follow up) and prevalent patients (who were known to the practice at baseline).

5.1 Non participants and endpoint data

At follow up, collected data was more accurate and complete for two reasons:

1. Two dedicated, independent, experienced researchers collected data. All eligible patients were identified and had their data collected.
2. The quantity and quality of computer recorded information was improved in 2005, as a result of the introduction of the GMS contract, which provided financial incentives for the creation and maintenance of computerised disease registers. This reduced the labour intensive task of finding and hand searching paper records for every patient, as had occurred at baseline.

Therefore, at follow up, a total of 7586 eligible patients (SOS: 4234; UC: 3352) were identified in 29 practices. These 7586 patients comprised 5660 patients (UC: 2425; SOS: 3235) with a first diagnoses of vascular disease before baseline and 1926 (UC: 927, SOS: 999) who were first diagnosed between baseline and follow up. From the 5660 patients identified at follow up who were found to have their first eligible diagnosis dated before baseline, 2619 were matched from baseline to follow up.

Table 5.1 describes the distribution of patients within the practice pairs matched at randomisation. Data in Table 5.1 and all subsequent Tables does not include values from the practice which had disbanded prior to the date of randomisation, or data from the practice which dropped out of the study (access to practice level data was not possible after this practice had dropped out).

Table 5.1 Distribution of eligible patients (by randomised pairs, according to date of first diagnosis)

Pair	Eligible at follow up (n = 7586)		Subgroup eligible before baseline (n = 5660 / 7586)		Subgroup eligible between baseline and follow up (n = 1926 / 7586)	
	SOS	UC	SOS	UC	SOS	UC
1	251	237	245	174	6	63
2	494	142	327	114	167	28
3	369	366	276	176	93	190
4	370	268	288	218	82	50
5	336	603	247	506	89	97
6	585	359	486	253	99	106
7	484	160	416	95	68	65
8	478	161	375	135	103	26
9	§	82	§	66	§	16
10	75	295	45	160	30	135
11	193	141	110	115	83	26
12	142	124	114	102	28	22
13	84	76	55	54	29	22
14	165	193	80	147	85	46
15	208	145	171	110	37	35
Subto tal	4234	3352	3235	2425	999	927
Total	7586		5660		1926	

§ Practice dropped out of study after first SOS visit (n = 57 patients); data not available at follow up

This subdivision of 7586 patients separates those known by the practice as eligible (through their diagnosis date) before baseline data collection or eligible after baseline data collection. Differentiating patients in this way enabled testing of the effectiveness of the intervention on these important subgroups, helping to address the question of whether the intervention was effective in improving the statin prescribing and cholesterol control of either, neither or both groups.

In 2006, due to advances in electronic recording and record linkage, the records of a sample of patients to be extracted from practices by a remote server based in the GG&C Information Technology centre, Gartnavel Royal Hospital. This facility enabled time to first new vascular diagnoses could be collected and evaluated for any differences between the SOS intervention and UC arms in the time to first event. This evaluation was applicable to 1911 (1078 from the SOS arm and 833 from UC arm) of the 5660 patients who had CHI recorded accurately, because this was the primary key for data linkage between baseline and follow up.

Compared to the number with CHI recorded at baseline, a greater number of patients had date of birth and gender recorded at baseline and this enabled a greater number to be traced from baseline to follow up. Therefore, 2619 patients were traced from baseline to follow up, as described in Table 5.2.

Table 5.2 Distribution of eligible patients known to practices at baseline and follow up

Randomised Pair	Linked from baseline to follow up (n =2619)	
	SOS	UC
1	162	88
2	197	67
3	164	84
4	154	96
5	135	142
6	140	80
7	173	51
8	49	77
9	§	40
10	24	101
11	70	49
12	59	58
13	29	30
14	39	98
15	96	67
Subtotal	1491	1128
Total	2619	

§ practice dropped out of study after first SOS visit (n = 57 patients)

Figure 5.1 summarises the relationships between subsets of patients identified at follow up. Categorising patients in this way enabled exploration of any differential effect from the SOS intervention e.g. on patients eligible at baseline ('Prevalent' in Fig 5.1: known to the practice for the whole period of the SOS study) compared with patients who became eligible after baseline data collection ('Incident'). From the 5660 patients identified at follow up who were found to have first diagnosis before baseline, 2619 patients were confirmed as being part of the cross section of 4040 collected at baseline. The remaining 1421 / 4040 patients from baseline (880 SOS and 541 UC), could not be matched to the records of patients identified at follow up. These patients are not accounted for in the main analyses. As it cannot be assumed that the characteristics of these 1421 patients are balanced between SOS and UC and balanced in comparison with the 2619 patients who were followed up, relevant summaries and analyses are described below.

The characteristics of the 1421 non participants are shown by their allocation to SOS or UC in Tables 5.2.1 to 5.2.3. Demographics and qualifying diagnoses were balanced between SOS and UC arms (Table 5.2.1).

Table 5.2.1 Baseline characteristics of non participants (SOS vs. UC): demographics and co-morbidities

	SOS (n = 880)	UC (n = 541)	p value
Mean age (SD), years [†]	70.5 (13.5)	70.2 (13.2)	0.41 ¹
Sex, male	412/880 (46.8%)	266/541 (49.2%)	0.39 ²
Qualifying diagnosis			
Values shown are number (%) of patients with each type of vascular disease			
Angina / Ischaemic Heart Disease	413/880 (47.1%)	246/541 (45.6%)	0.71 ²
Diabetes Mellitus, age ≥ 45 years	253/880 (28.7%)	152/541 (28.1%)	0.51 ²
MI	171/880 (19.4%)	107/541 (19.8%)	0.63 ²
Cerebrovascular event	152/880 (17.3%)	114/541 (21.1%)	0.09 ²
PVD	103/880 (11.7%)	63/540 (11.7%)	0.68 ²
TIA	81/880 (9.2%)	61/540 (11.3%)	0.21 ²
CABG	48/880 (5.5%)	37/541 (6.8%)	0.30 ²
Angioplasty	28/880 (3.2%)	10/541 (1.9%)	0.08 ²
Number of vascular co-morbidities [†]	1.42 (0.78)	1.46 (0.72)	0.20 ¹
Number of vascular co-morbidities excepting angina [†]	0.95 (0.72)	1.00 (0.66)	0.18 ¹

¹Linear regression ²Binary logistic regression [†] Mean (SD)

Table 5.2.2 provides further supporting evidence that there was no statistically significant difference between the characteristics of non participants in SOS compared with UC arms.

Table 5.2.2 Baseline characteristics of non-participants (SOS vs. UC): cholesterol

	SOS (n = 880)	UC (n = 541)	p value
Statin prescribing and cholesterol			
Cholesterol recorded	578/880 (65.4%)	339/541 (62.7 %)	0.20 ²
Cholesterol recorded and controlled	279/880 (31.7%)	156/541 (28.8%)	0.45 ²
Cholesterol level (mmol/l), all patients with cholesterol level †	4.99 (1.3)	5.06 (1.2)	0.36 ¹
Cholesterol level (mmol/l), all patients with cholesterol recorded and prescribed a statin †	4.88 (1.3)	4.96 (1.3)	0.40 ¹
Cholesterol level (mmol/l), all patients with cholesterol recorded and not prescribed a statin †	5.08 (1.2)	5.13 (1.2)	0.71 ¹
Statin not prescribed	607/880 (68.9%)	377/541 (69.7%)	0.68 ²
Statin prescribed at optimal dose	156/880 (17.7%)	82/541 (15.1%)	0.45 ²

¹ Linear regression ² Binary logistic regression † Mean (SD)

Table 5.2.3 summarises Simvastatin prescribing, cholesterol control and cholesterol levels for all non participants, by treatment group.

Table 5.2.3 Characteristics at baseline of non participants prescribed a statin (SOS vs. UC)

	SOS (n = 273)	UC (n = 164)	p value	
Cholesterol not recorded	34/273 (12.5%)	29/164 (17.7%)	0.13 ²	
Cholesterol recorded and controlled	126/239 (52.7%)	62/135 (45.9%)	0.26 ²	
Simvastatin	All doses	158/273 (57.9%)	102/164 (62.2%)	0.58 ²
	Suboptimal dose	100/273 (36.6%)	65/164 (39.6%)	0.76 ²
	Optimal dose, cholesterol controlled	21/723 (7.7%)	14/164 (8.5%)	0.93 ²
	All doses, cholesterol controlled	71/273 (26.0%)	43/164 (26.2%)	0.47 ²
	Mean Cholesterol level (mmol/l) †	4.82 (1.27)	4.79 (1.25)	0.93 ¹

¹ Linear regression ² Binary logistic regression † Mean (SD)

Overall, the characteristics of non participants appear balanced between SOS and UC arms.

Characteristics of non participants (n = 1421) are compared with participants who were tracked from baseline to follow up (n = 2169), in Tables 5.2.4 and 5.2.5.

Table 5.2.4 Baseline comparison of 1421 patients lost to follow up and 2169 patients included at follow up: demographics and qualifying diagnoses

	Participants (n = 2169 tracked from baseline to follow up)	Non participants (n = 1421 not tracked from baseline to follow up)	p value
Age (years) [†]	67.2 (11.1)	70.4 (13.7)	< 0.001 ¹
Sex, male	1418/2169 (54.1%)	678/1421 (47.7%)	< 0.001 ²
Qualifying diagnosis			
Values shown are number (%) of patients with each type of vascular disease			
Angina / Ischaemic Heart Disease	1184/2169 (45.2%)	659/1421 (40.4%)	0.480 ¹
Diabetes Mellitus, age ≥ 45 years	1067/2169 (40.7%)	405/1421 (28.5%)	< 0.001 ¹
MI	573/2169 (21.9%)	278/1421 (19.6%)	0.080 ¹
Cerebrovascular event	304/2169 (11.6%)	266/1421 (18.7%)	< 0.001 ¹
PVD	281/2169 (10.7%)	166/1421 (11.7%)	0.360 ¹
TIA	202/2169 (7.7%)	142/1421 (10.0%)	0.013 ¹
CABG	258/2169 (9.8%)	85/1421 (6.0%)	< 0.001 ¹
Angioplasty	133/2169 (5.1%)	38/1421 (2.7%)	< 0.001 ¹
Number of vascular co-morbidities [†]	1.52 (0.78)	1.44 (0.74)	< 0.001 ²
Number of vascular co-morbidities excepting angina [†]	1.08 (0.69)	0.98 (0.68)	< 0.001 ²

[†] Mean (SD) ¹ Chi squared test ² Two sample t-test

These results suggest patients who were included at baseline but not traced to follow up were likely to be older and female. There were statistically significant differences in all eligible diagnoses except angina/ischaemic heart disease, myocardial infarction and peripheral vascular disease. However, prevalence was greater in some cases (stroke, transient ischaemic attack) and lower in others (diabetes, coronary bypass graft and angioplasty). Non participants had fewer multiple co-morbidities.

Table 5.2.5 Baseline comparison of 1421 non participants and 2169 patients included at follow up: statin prescribing and cholesterol

	Participants (n = 2619 tracked from baseline to follow up)	Non participants (n = 1421 not tracked from baseline to follow up)	p value
Cholesterol recorded	2153/2619 (82.2%)	913/1421 (64.2%)	< 0.001 ¹
Cholesterol recorded and controlled	1115/2619 (42.5%)	435/1421 (30.6%)	< 0.001 ¹
Cholesterol level (mmol/l), all patients with cholesterol tested [†]	4.89 (1.24)	5.02 (1.25)	0.005 ²
Mean cholesterol level (mmol/l), all patients with cholesterol recorded and not prescribed a statin [†]	5.10 (1.22)	5.10 (1.24)	0.979 ²
Statin not prescribed	1402/2619 (53.5%)	984/1421 (69.3%)	< 0.001 ¹
Patients prescribed a statin			
Statin prescribed at optimal dose	694/2619 (26.5%)	238/1421 (16.7%)	< 0.001 ¹
Cholesterol not recorded	101/2619 (3.9%)	63/1421 (4.4%)	0.375 ¹
Cholesterol recorded and controlled	647/2619 (24.7%)	188/1421 (13.2%)	< 0.001
Cholesterol level (mmol/l), all patients with cholesterol recorded and prescribed a statin [†]	4.71 (1.25)	4.91 (1.27)	0.004 ²
Patients prescribed Simvastatin			
All doses	709/2619 (27.1%)	260/1421 (18.3%)	< 0.001 ¹
Suboptimal dose	439/2619 (16.8%)	165/1421 (11.6%)	< 0.001 ¹
Optimal dose, cholesterol controlled	128/2619 (4.9%)	35/1421 (2.5%)	< 0.001 ¹
All doses, cholesterol controlled	370/2619 (14.1%)	114/1421 (8.0%)	< 0.001 ¹
Cholesterol level [†]	4.72 (1.26)	4.81mmol/l (1.26)	0.275 ²

[†] Mean (SD) ¹ Chi squared test ² Two sample t-test

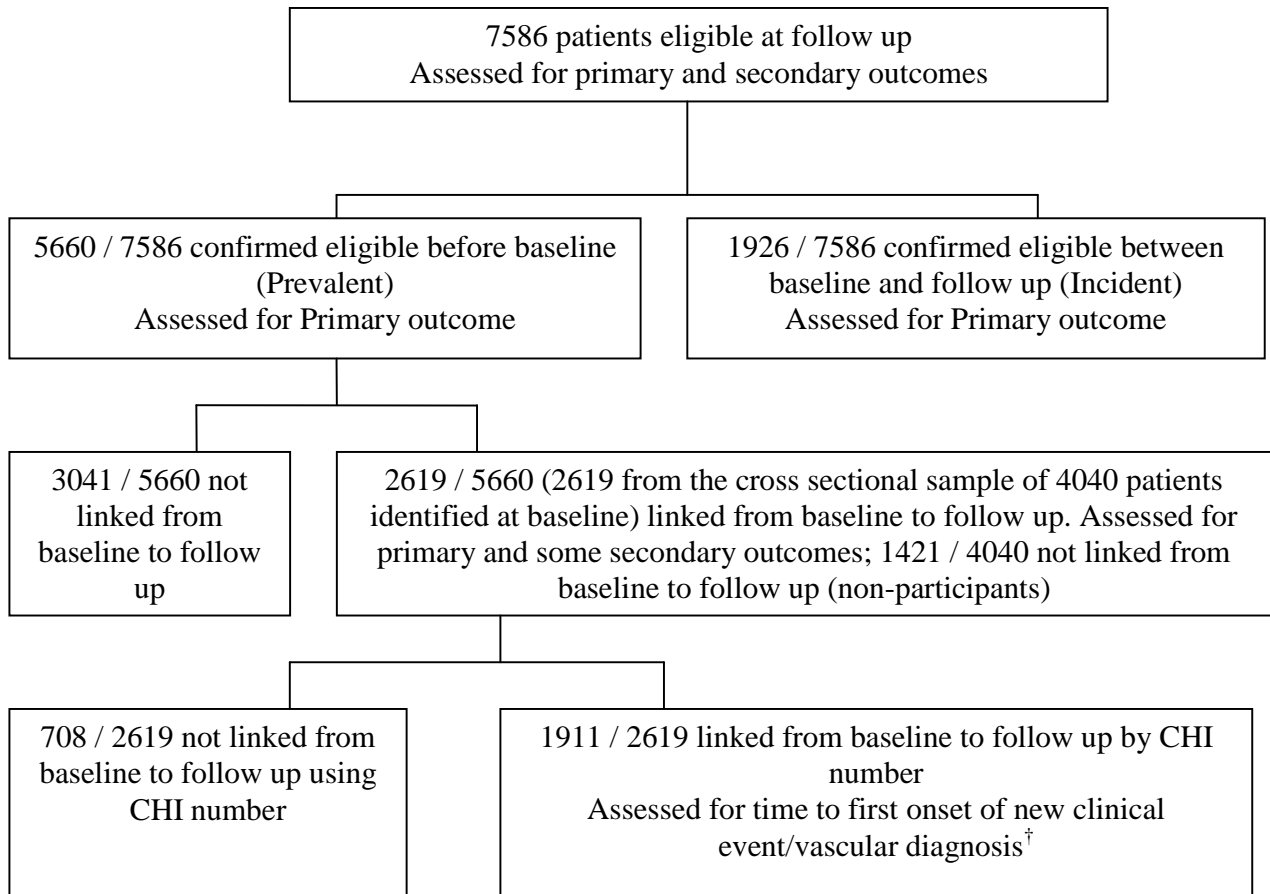
Table 5.2.5 describes statistically significant differences between patients who were not followed up compared with those who were traced to follow up. These differences extended across statin prescribing, cholesterol recording and control. Non participants had less recording of their cholesterol, less control but statistically significantly higher cholesterol (although the magnitude of this difference (0.1mmol/l) is not likely to represent a clinically significant difference in practice. A higher proportion of non participants were not prescribed a statin at baseline. Of those prescribed a statin, a lower proportion were prescribed optimal dose and a lower proportion had controlled cholesterol. The greater mean cholesterol level of non participants prescribed a statin reached statistical significance however, the magnitude of

the difference (0.2mmol/l) may not be of clinical importance. A similar trend was shown for patients prescribed simvastatin.

Together, these results suggest there were differences between participants and non participants.

The extent to which non participants were missing from follow up because of premature death was investigated using original baseline records. Of the 1421 non participants, 1168 (773 / 880 (87.8%) SOS and 395 / 541 (73.0%) UC; $p < 0.001$) had sufficient demographic data to enable determination of whether they were alive or dead at the end of the study. These data showed that 507/773 (65.6%) from SOS and 263/395 (66.6%) from UC were alive at least until the date of follow up within their practice pair. Binary logistic regression gave an odds ratio of 1.04 (95% CI 0.79 – 1.38; $p = 0.76$) suggesting no statistically significant difference between SOS and UC, in the proportion of patients dying prematurely during the study. The mean duration of follow up was 1.7 years (range 1.4 to 2.2 years) and during that period, a high proportion (34%) of patients died prematurely. While this represents a rate of premature mortality in excess of that noted in the population enrolled in the Heart Protection Study (Table 2.2), these results represent mortality among an unselected primary care based population. In addition, limitations of the post-hoc analysis include uncertain accuracy and completeness of baseline demographic data for non participants.

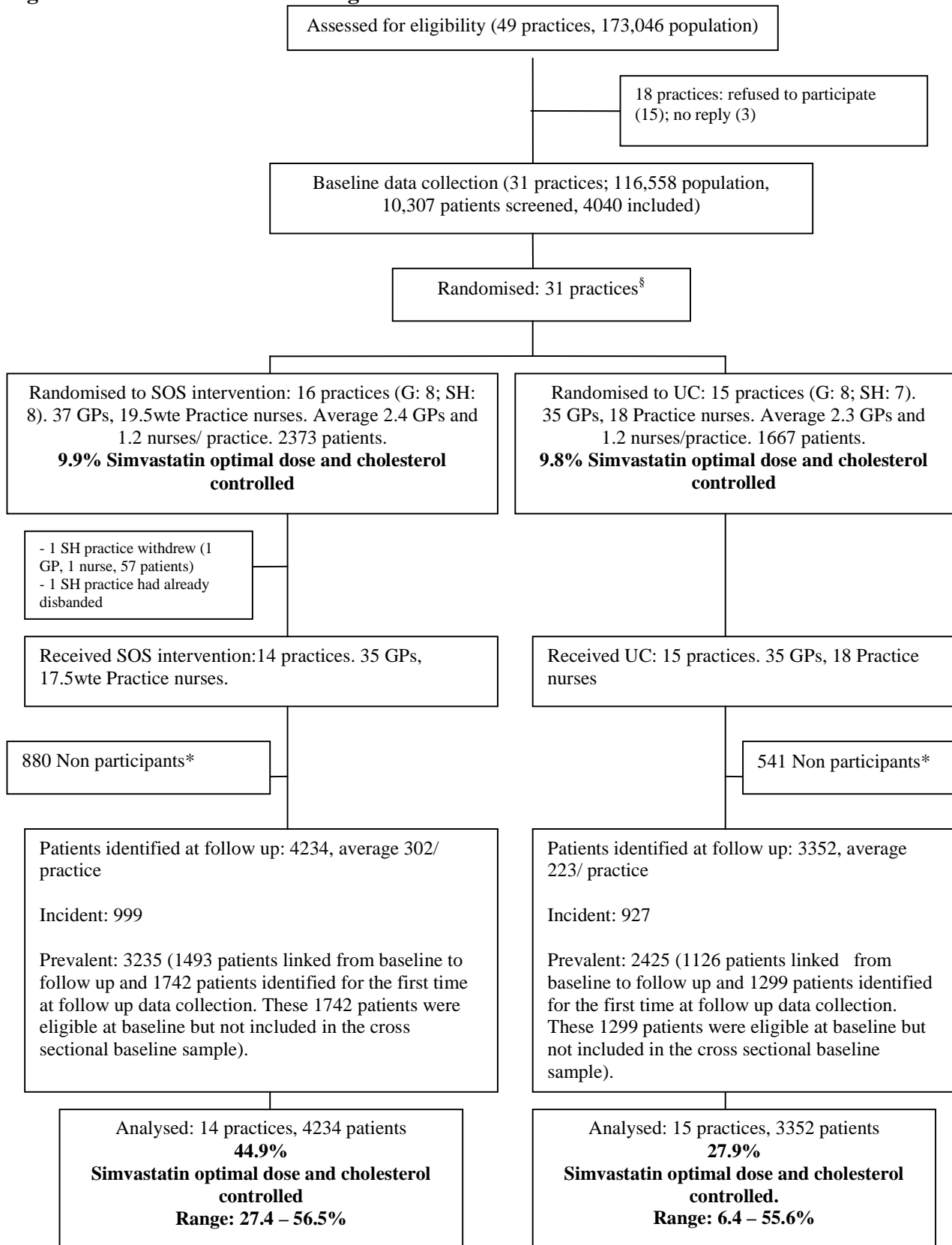
Figure 5.1 Inter-relationships of subgroups of 7586 patients at follow up



†MI, stroke, TIA, diabetes, angina, CABG, Angioplasty, PVD/Claudication.

Figure 5.2 gives the CONSORT flow diagram (Campbell 2004) for the passage of practices and patients through the study.

Fig 5.2 CONSORT flow diagram



[§] 31 practices were randomised; one had already disbanded prior to the randomisation date. * excluded from follow up analysis due to insufficient baseline data or premature mortality, which precluded linkage to follow up.

5.2 Primary outcome: Prescribed simvastatin 40mg and cholesterol controlled

Table 5.3 Primary outcome for all patients (n = 7586)

Pair (n)	UC[†]	SOS[†]	Odds Ratio	95% Confidence Interval	p-value[‡]
1 (488)	82/237 (34.6%)	89/251 (35.5%)	1.04	0.72, 1.51	0.842
2 (636)	65/142 (45.8%)	229/494 (46.4%)	1.02	0.70, 1.49	0.903
3 (735)	43/366 (11.7%)	132/369 (35.8%)	4.18	2.85, 6.13	<0.001
4 (638)	149/268 (55.6%)	159/370 (43.0%)	0.60	0.44, 0.83	0.002
5 (939)	202/603 (33.5%)	139/336 (41.4%)	1.40	1.06, 1.84	0.016
6 (944)	85/359 (23.7%)	310/585 (53.0%)	3.63	2.71, 4.87	<0.001
7 (644)	46/160 (28.8%)	248/484 (51.2%)	2.60	1.77, 3.83	<0.001
8 (639)	62/161 (38.5%)	270/478 (56.5%)	2.07	1.44, 2.99	<0.001
9 (82)	7/82 (8.5%)	Practice dropped out			
10 (370)	19/295 (6.4%)	21/75 (28.0%)	5.65	2.85, 11.21	<0.001
11 (334)	41/141 (29.1%)	56/193 (29.0%)	1.00	0.62, 1.61	0.990
12 (266)	34/124 (27.4%)	76/142 (53.5%)	3.05	1.82, 5.10	<0.001
13 (160)	21/76 (27.6%)	31/84 (36.9%)	1.53	0.78, 2.99	0.212
14 (358)	30/193 (15.5%)	82/165 (49.7%)	5.37	3.27, 8.80	<0.001
15 (353)	49/145 (33.8%)	57/208 (27.4%)	0.74	0.47, 1.17	0.198
All (7586)	935/3352 (27.9%)	1899/4234 (44.9%)	1.79	1.61, 1.98	<0.001
Range	6.4 – 55.6%	27.4 – 56.5%			

[†] n achieving primary outcome / n eligible (%) [‡] Fixed effects, adjusted The ICC for the primary outcome was 0.05.

Primary analysis

Table 5.3 shows the SOS intervention achieved a statistically significant increase in the primary outcome (simvastatin 40mg prescribed and cholesterol controlled at follow up). This finding was consistent across fixed and random effects models, using adjusted and unadjusted analyses. The change favoured UC in one pair and favoured SOS intervention in 8 pairs. There was no significant difference in 5 pairs. The range of values of the primary outcome was greater across UC practices than in the SOS arm practices, suggesting the SOS intervention may have had the unexpected and useful effect of reducing variation across practices.

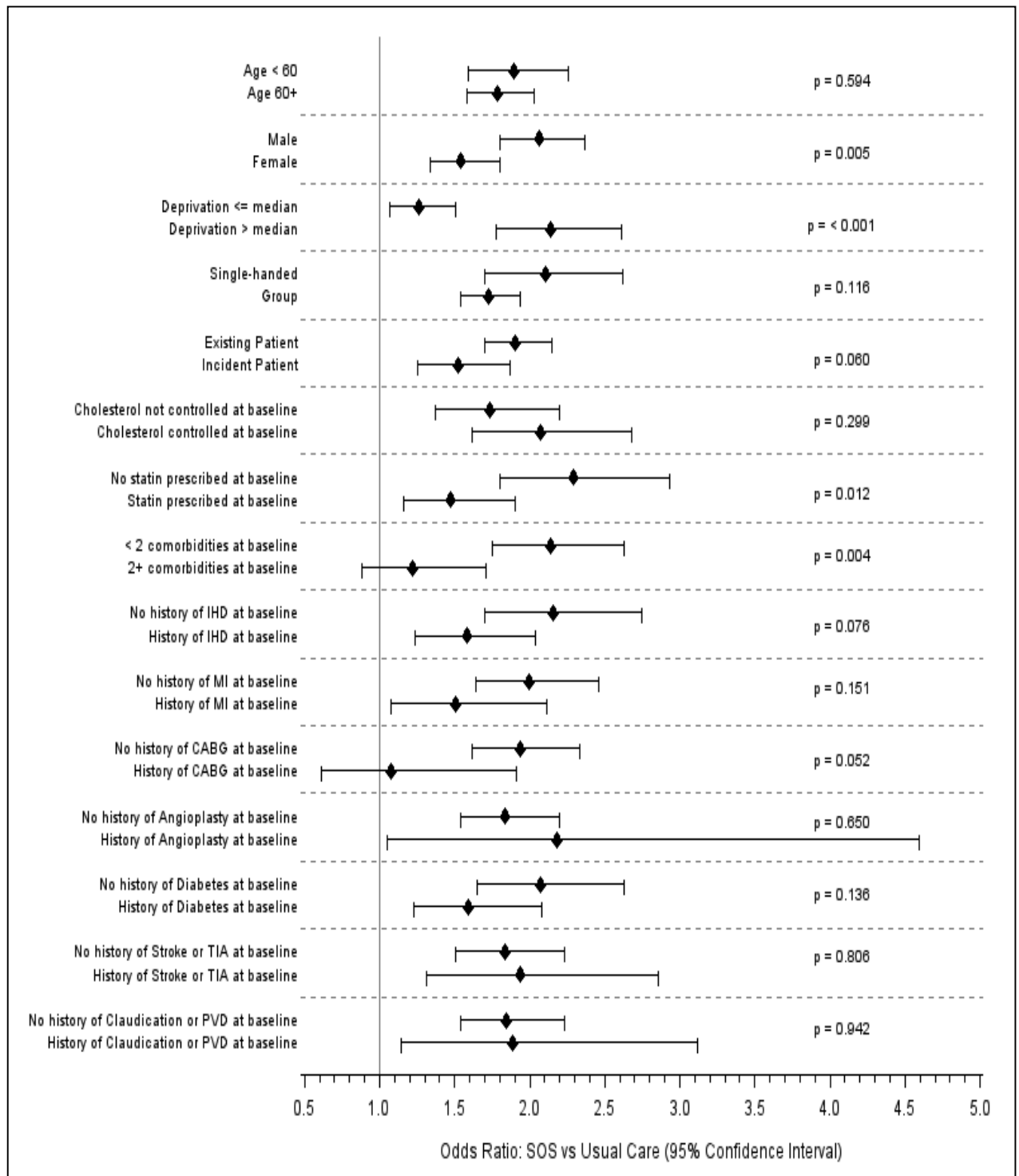
5.2.1 Subgroup analyses of the primary outcome for all patients at follow up (n = 7586)

Table 5.4 Subgroup analyses of the primary outcome

Subgroup	UC	SOS	Odds Ratio	95% CI	p-value for SOS effect within subgroup	p-value for differences between subgroups
Practice level						
Deprivation ≤ median [§]	657/2394 (27.4%)	524/1356 (38.6%)	1.24	1.04, 1.47	0.014	< 0.001
Deprivation > median [§]	278/958 (29.0%)	1375/2878 (47.8%)	2.17	1.79, 2.63	< 0.001	
Single Handed practices	201/1056 (19.0%)	323/867 (37.3%)	2.02	1.63, 2.51	< 0.001	0.206
Group practices	734/2296 (32.0%)	1576/3367 (46.8%)	1.72	1.53, 1.94	< 0.001	
Patient level						
Male	518/1835 (28.2%)	1094/2256 (48.5%)	2.04	1.78, 2.34	< 0.001	0.005
Female	417/1517 (27.5%)	805/1978 (40.7%)	1.53	1.32, 1.78	< 0.001	
≤ 60 years	306/1166 (26.2%)	628/1374 (45.7%)	1.87	1.56, 2.23	< 0.001	0.631
> 60 years	629/2186 (28.8%)	1249/2777 (45.0%)	1.77	1.56, 2.01	< 0.001	
Eligible before baseline (n = 5660)	688/2425 (28.4%)	1485/3235 (45.9%)	1.89	1.68, 2.13	< 0.001	0.056
Eligible after baseline (n = 1926)	247/927 (26.6%)	414/999 (41.4%)	1.51	1.23, 1.84	< 0.001	

[§] practice level modified Scottish Index of Multiple Deprivation. Increased mSIMD scores reflect greater levels of deprivation.

Table results in Table 5.4 indicate the SOS intervention was effective ($p < 0.001$) in nine subgroups, with a p-value of 0.014 in one subgroup (deprivation equal to, or lower than the median value). Odds ratios were consistently greater than 1, indicating a favourable effect from SOS intervention on the primary outcome; the same effect was observed in all other subgroups, as shown in the forest plot (Figure 5.3). Results of the following subgroups will be described in more detail: deprivation, practice type, gender/age and eligible before/after randomisation.

Figure 5.3 Subgroup analyses of primary outcome

'Existing': eligible at baseline. 'Incident': eligible after baseline.

Point estimates of Odds Ratios to the right of 1 represent favourable effect of the SOS intervention

5.2.1.1 Socioeconomic deprivation

The modified Scottish Index of Multiple Deprivation (mSIMD) score gives a measure of the level of socioeconomic deprivation in a practice, relative to other practices in Scotland. As described in Chapter 3, study practices were categorised as less than or equal to the median mSIMD or above the median mSIMD. Table 5.4 gives the effect of the SOS intervention compared with UC, evaluated within each category ('p-value for SOS effect within subgroup'). The intervention effect estimate within each category was then compared between categories ('p-value for differences between subgroups'). The results show an improvement due to the SOS intervention within each category, and a statistically significant interaction (in favour of practices falling into the more deprived category) between deprivation categories, in the proportions of patients receiving simvastatin 40mg with their cholesterol controlled. This finding suggests the SOS intervention tackles a small, but important manifestation of the inverse care law (Hart 1971).

5.2.1.2 Practice type

We hypothesised there would be a difference in the uptake of the SOS intervention's educational messages depending on whether practices were Single Handed or Group. This was one of the stratification variables (the other stratification variable was the proportion of patients with cholesterol controlled in each practice). The primary outcome was achieved to a greater extent in Group (SOS 46.8%) compared with Single Handed practices (37.3%) as described in Table 5.4. However there was also a difference in UC (G: 32.0% vs. SH: 19.0%) hence there was no statistically significant difference in the intervention effect estimate between Group and Single Handed practices ($p = 0.206$).

At baseline, we noted a higher prevalence of diabetes in four Single Handed practices caring for patients within communities with predominantly residents of South Asian origin. Randomisation led to allocation of two practices to the SOS arm and two practices to UC. However, the SOS allocated practices had fewer eligible patients and had a lower proportion of patients with diabetes compared with the UC allocated practices within South Asian communities (SOS proportions with diabetes: 154/203 (75.9%); UC: 419/488 (85.9%). $X^2 = 10.1$; $p = 0.001$). This test of association indicates an imbalance in the proportions of patients with diabetes in these practices however it is often the case in trials with a small number of clusters and stratified randomisation, that there are imbalances in baseline variables other than those factored into the stratification process.

For patients with diabetes, subgroup analysis of the primary outcome (Figure 5.3) showed no interaction compared with non-diabetic patients (p value for interaction 0.136). The intervention improved simvastatin 40mg prescribing and cholesterol control for both. In the four practices serving South Asian communities, the two practices allocated to SOS also fared better in relation to the primary outcome (mean 33.6%) compared with the two South Asian practices allocated to UC (mean primary outcome 11%).

5.2.1.3 Gender and age

Both males and females received improved prescribing of simvastatin 40mg with controlled cholesterol, but there was a larger benefit for males ($p = 0.005$ for interaction).

The SOS intervention achieved a statistically significant, positive impact in both age categories (≤ 60 years and > 60 years), with no evidence of interaction between subgroups defined by this age division (Table 5.4 or Figure 5.3).

5.2.1.4 Eligible before vs. after randomisation

The primary outcome was achieved to a greater extent in the SOS arm practices compared with UC practices, for the group of patients eligible before and for the group of patients eligible after baseline. There was some evidence of the SOS intervention having a even greater impact on those eligible before baseline as compared with patients who became eligible after baseline ($p = 0.056$). A preferential effect on those eligible before baseline might be expected: practices had a longer time to improve prescribing and cholesterol management for these patients, compared with those identified as eligible at some point after baseline. In addition, the 2619 patients known at baseline who were tracked to follow up represent patients who (in theory) had the best chance of improvement through the SOS intervention, because they were known to the practice at baseline and confirmed as being alive and registered with the practice at follow up. The impact of the intervention on 2619 patients known to the practice from baseline to follow up is described below.

5.2.2 Subgroup analyses of primary outcome for subgroup linked from baseline to follow up (n = 2619)

Table 5.5 shows the results of subgroup analyses on those patients who were linked from baseline to follow up (n = 2619). These indicate a favourable effect on the primary outcome, for 6 of the 8 subgroups shown. These analyses identified 2 subgroups where the SOS intervention did not have a statistically significant effect: patients with more 3 or more vascular diagnoses and those with a previous coronary artery bypass graft. The following four subgroups are described in more detail below: cholesterol controlled/uncontrolled at baseline, prescription/no prescription of a statin at baseline, number of vascular diagnoses at baseline and presence/absence of CABG.

Table 5.5 Subgroup analyses of primary outcome, for patients linked from baseline to follow up (n = 2619)

Subgroup	UC	SOS	Odds Ratio	95% CI	p-value for SOS effect within subgroup	p-value for differences between subgroups
Uncontrolled cholesterol at baseline	158/628 (25.2%)	346/867 (39.9%)	1.67	1.32, 2.12	< 0.001	0.260
Controlled cholesterol at baseline	166/500 (33.2%)	333/624 (53.4%)	2.04	1.58, 2.62	< 0.001	
No statin prescribed at baseline	148/579 (25.6%)	389/823 (47.3%)	2.21	1.73, 2.82	< 0.001	0.015
Statin prescribed at baseline	176/549 (32.1%)	290/668 (43.4%)	1.45	1.13, 1.85	0.003	
≤ 2 vascular diagnoses	227/866 (26.2%)	508/1104 (46.0%)	2.09	1.70, 2.55	< 0.001	0.004
> 2 vascular diagnoses	97/262 (37.0%)	171/387 (44.2%)	1.19	0.85, 1.66	0.309	
Patients with no CABG	293/1008 (29.1%)	639/1357 (47.1%)	1.89	1.57, 2.27	< 0.001	0.049
Patients with a CABG	31/120 (25.8%)	40/134 (29.9%)	1.04	0.59, 1.84	0.890	

5.2.2.1 Cholesterol controlled vs. uncontrolled at baseline

From Table 5.5, in the subgroup of patients who had uncontrolled cholesterol at baseline, the SOS intervention achieved the primary outcome for 39.9% of patients at follow up, compared with 25.2% in the UC group (OR 1.67, CI: 1.32 – 2.12; $p < 0.001$). Patients with uncontrolled cholesterol had more to gain from the SOS intervention, and the favourable effect is likely to have reduced their vascular event risk.

5.2.2.2 Patients with or without a statin at baseline

In Table 5.5, we determined if there was any interaction, because during pilot work, some practices had suggested they would not benefit from the SOS intervention due to their perception of their practice having high baseline prescribing of statins. We therefore tested for any difference in the extent of uptake of the SOS intervention in the subgroup of patients with statins prescribed at entry to the study, compared with those without. Our expectation was for a relatively greater effect from the SOS intervention on the primary outcome in patients

without statins at baseline, because these patients had more to gain and the expectation was for practices to prioritise their management.

The results shown in Table 5.5 confirmed a greater effect from the SOS intervention ($p = 0.015$) on patients without a statin at baseline. These patients were more than twice as likely to achieve the primary endpoint compared with patients in the UC group.

However, contrary to the expectations of several GPs in practices with high baseline statin prescribing, patients prescribed a statin at baseline also benefited (in terms of the primary endpoint) with an odds ratio of 1.45 (95% CI: 1.13 to 1.95). The intervention effect estimate between categories reached significance ($p = 0.015$). A Chi – squared test of the primary outcome between ‘statin’ and ‘no statin’ groups in the SOS intervention arm did not show statistical significance ($X^2 = 2.05$; $p = 0.15$). This suggests that the primary outcome rate in SOS practices was similar for patients who were not on a statin at baseline compared to those who were.

5.2.2.3 Number of vascular diagnoses at baseline

We also determined if there was any difference in the uptake of the SOS intervention as measured by the primary outcome, between patients with two or less vascular diagnoses at baseline compared with more than two vascular diagnoses at baseline. There was some evidence of the SOS intervention having a significantly stronger influence on the primary outcome for patients with less vascular co-morbidities compared to those with more (OR 2.09 vs. 1.19; p value for difference 0.004; Table 5.5). Of some concern was the finding that the intervention failed to demonstrate effect in those patients with three or more vascular co-morbidities.

Table 5.5 shows there was no evidence of effect from the SOS intervention on the subgroup of linked patients with more than 2 vascular diagnoses. While there is insufficient information to say why this was the case, it is possible that the relatively high proportion of patients already achieving the primary outcome in the UC group (37.0%) represented a value close to the ceiling level achieved through SOS intervention (44.2%). This suggests there was less room for the SOS intervention to increase the primary outcome. It is possible that patients with more vascular diagnoses are subject to more frequent call/recall in primary care and contact with secondary care clinics, thus increasing their chances of attaining cholesterol control and receiving a prescription for simvastatin 40mg, compared with patients who had 2 or less. In absolute terms, if the upper limit of the SOS intervention effect on simvastatin 40mg and cholesterol control is between 37% and 44% for patients with more than 2 vascular co-morbidities. This perhaps represents a limitation of the model. Further analysis is required to explore whether this result signals a trend of a drop in effectiveness in proportion to the number of vascular co-morbidities.

5.2.2.4 Coronary Artery Bypass Graft

There is some evidence from the published literature that prescribing of statins is up to four times higher in revascularised patients compared with patients with Angina (De Wilde 2003). This might be an expected consequence of the need for tighter cholesterol targets for this

group as compared with others (the target cholesterol level for patients with a CABG is less than 4.2mmol/l). Therefore we determined if there were any significant differences in the uptake of the SOS intervention in this subgroup compared with the rest of the sample, as judged by the primary outcome measure.

The impact of the SOS intervention was found to be negligible in those patients with previous CABG (Table 5.5): SOS 40/134 (29.9%) vs. UC 31/120 (25.8%) Odds Ratio 1.04 (CI: 0.59 – 1.84). This follows from the unusually tight control of cholesterol and higher level of statin prescribing at baseline in this subgroup, perhaps indicating the SOS intervention is less successful when the baseline levels of cholesterol control and statin prescribing are already relatively high. However, the data show that the primary outcome was between 25 and 30% in UC and SOS arms, which was lower than the value of the primary outcome in most other subgroups. Therefore the explanation for this result is not clear from our data.

5.3 Secondary outcomes

The SOS intervention had a statistically significant, positive effect in each of the secondary outcomes (Table 5.6), except cholesterol levels of patients prescribed simvastatin 40mg at follow up.

Table 5.6 Secondary outcomes at follow up (all patients, n = 7586)

Secondary outcome	SOS* n = 4234 (number (%; range))	UC* n = 3352 (number (%; range))	OR	95% CI	p-value [§]
Prescribed simvastatin 40mg	2497 (58.9%; 30.7 – 71.1%)	1267 (37.8%; 15.2 - 65.7%)	2.06	1.87, 2.28	<0.001
Prescribed simvastatin (any dose)	2673 (63.1%; 42.3 – 73.4%)	1730 (51.6%; 31.2 – 73.7%)	1.60	1.46, 1.75	<0.001
Prescribed any statin, any dose	3682 (86.9%; 68.0 – 93.6%)	2509 (74.9%; 47.1 – 93.8%)	1.82	1.60, 2.06	<0.001
Prescribed simvastatin 40mg and cholesterol tested since baseline	2344 (55.4%; 25.3 – 66.1%)	1203 (35.9%; 13.2 – 64.5%)	1.80	1.61, 2.00	<0.001
Cholesterol level, patients prescribed simvastatin 40mg	4.06mmol/l [†] (3.60 – 4.40mmol/l)	4.15mmol/l [†] (3.54 – 4.52mmol/l)	0.99	0.97, 1.01	0.221
Cholesterol tested since baseline	3869 (91.4%; 72.5 – 98.8%)	2932 (87.5%; 65.8 – 97.4%)	1.26	1.07, 1.48	0.005
Cholesterol controlled	2943/4234 (69.5%; 49.4 – 77.5%)	2132 (63.6%; 35.6 – 83.4%)	1.11	1.00, 1.23	0.046
Mean cholesterol level (all patients) [†]	4.22mmol/l (4.03 – 4.48mmol/l)	4.36mmol/l (3.82 – 4.95mmol/l)	0.98	0.97, 0.99	0.005

* all pairs (28 practices, 14 pairs; 3352 SOS arm, 4234 UC) [§] fixed effects, adjusted [†] mean (range)

A more convincing effect from the SOS intervention was apparent in those outcomes incorporating a measure of statin prescribing e.g. simvastatin or any statin, any dose.

Combining all the secondary outcomes gave an adjusted odds ratio of 1.92 (95% confidence interval 1.72 to 2.13; $p < 0.001$), indicating the strength of the SOS intervention on a range of prescribing and cholesterol related endpoints, 1.7 years post randomisation.

The SOS intervention did achieve a statistically significant reduction in cholesterol levels. This may indicate the efficacy of simvastatin 40mg on patients who were prescribed it and adhered to their prescription, in both arms of the study.

The ranges for each of the secondary outcomes are given in Table 5.6. Ranges in the SOS arm practices were consistently tighter than in UC practices. A similar picture was found in response to the SOS intervention effect on the primary outcome (Table 5.3).

5.3.1 Subgroup analyses of secondary outcomes

For each of the secondary outcomes, the effect of the SOS intervention on a pre-specified list of subgroups was analysed to determine if there were any particular strengths or weaknesses in the effect of the SOS intervention, which might inform service roll out of the intervention, depending on the needs of different practices and their patient subgroups. Summaries of these analyses are shown in the forest plots represented in figures 5.4 to 5.11. Selected findings with consistent results across the secondary outcomes are described below.

5.3.1.1 Socioeconomic deprivation

A disproportionately greater SOS intervention effect in patients from practices in areas of greater socioeconomic deprivation was apparent in relation to the following secondary outcomes: prescribing of simvastatin 40mg (Figure 5.4), prescribing of simvastatin (Figure 5.5), prescribing of simvastatin 40mg and cholesterol tested (Figure 5.7), cholesterol levels of patients prescribed simvastatin 40mg (Figure 5.8) and the mean cholesterol level (Figure 5.11). These findings reinforced the primary outcome result. The intervention was therefore strong enough to show improvement in the (theoretically) more challenging secondary outcomes including cholesterol levels checked and achieved, both of which are several steps removed from the targeted behavioural change at practice level. This was a surprise finding. Taken together, these results may originate from the increased awareness among study pharmacists of the limitations of previous interventions for patients from practices in more socioeconomically deprived areas, and the pharmacists' additional efforts to overcome these during the delivery of the intervention to practices in more deprived areas. This (inverse) socioeconomic gradient was reversed in only two secondary outcomes: the SOS intervention favoured practices with patients from less deprived areas in relation to cholesterol levels tested for all patients (p -value < 0.001 ; Figure 5.9) and cholesterol levels on simvastatin 40mg (Figure 5.8).

5.3.1.2 Practice type

There were statistically significant differences in four secondary outcomes when Single Handed practices were compared with Group practices and three of these outcomes were favourable for Single Handed practices: cholesterol levels of patients prescribed simvastatin

40mg (Figure 5.8); proportions receiving cholesterol checks (Figure 5.9) and those with cholesterol controlled (Figure 5.10). Prescribing of simvastatin (Figure 5.5) favoured patients in Group practices. The favourable findings may be of use for Single Handed practices with particularly low levels of achievement in relation to these variables, if the SOS intervention is subsequently rolled out. One report suggested that small or Single Handed practices may have more difficulty achieving QoF organisational domain points, compared with larger practices (Wang 2006). With our results showing greater improvement in some secondary outcomes and general improvement in all outcomes, the SOS intervention demonstrates how statin prescribing inertia (whatever the root cause) can be overcome.

5.3.1.3 Gender and age

In relation to gender, all secondary outcomes appeared to be reached to a greater extent by males, except 'cholesterol levels tested' (Figure 5.9) and cholesterol levels controlled (Figure 5.10). The predominantly greater benefit in males was also a surprise finding.

Age (60 years and younger compared with over 60 years) was considered in our subgroup analyses because there is some published evidence suggesting ageism in the prescribing of statins (De Wilde 2001). Using our arbitrary threshold of 60 years, we found no evidence supporting this finding.

5.3.1.4 Other subgroups

Patients eligible before or after baseline were considered in the subgroup analysis. On evaluating any differential SOS intervention effect for the secondary outcomes, the following were significant ($p < 0.05$), all in favour of patients identified at baseline:

- Prescribing of any statin;
- Cholesterol levels tested;
- Cholesterol levels controlled.

For the subgroup with a history of revascularisation, analyses of the secondary outcomes suggested no clear pattern of a differential impact of the SOS intervention. The wide confidence intervals displayed for both subgroups (CABG and angioplasty) across all outcomes may be due to the relatively small numbers of patients with these diagnoses.

Figure 5.4 Subgroup analyses of secondary outcome: Prescribing of Simvastatin 40mg

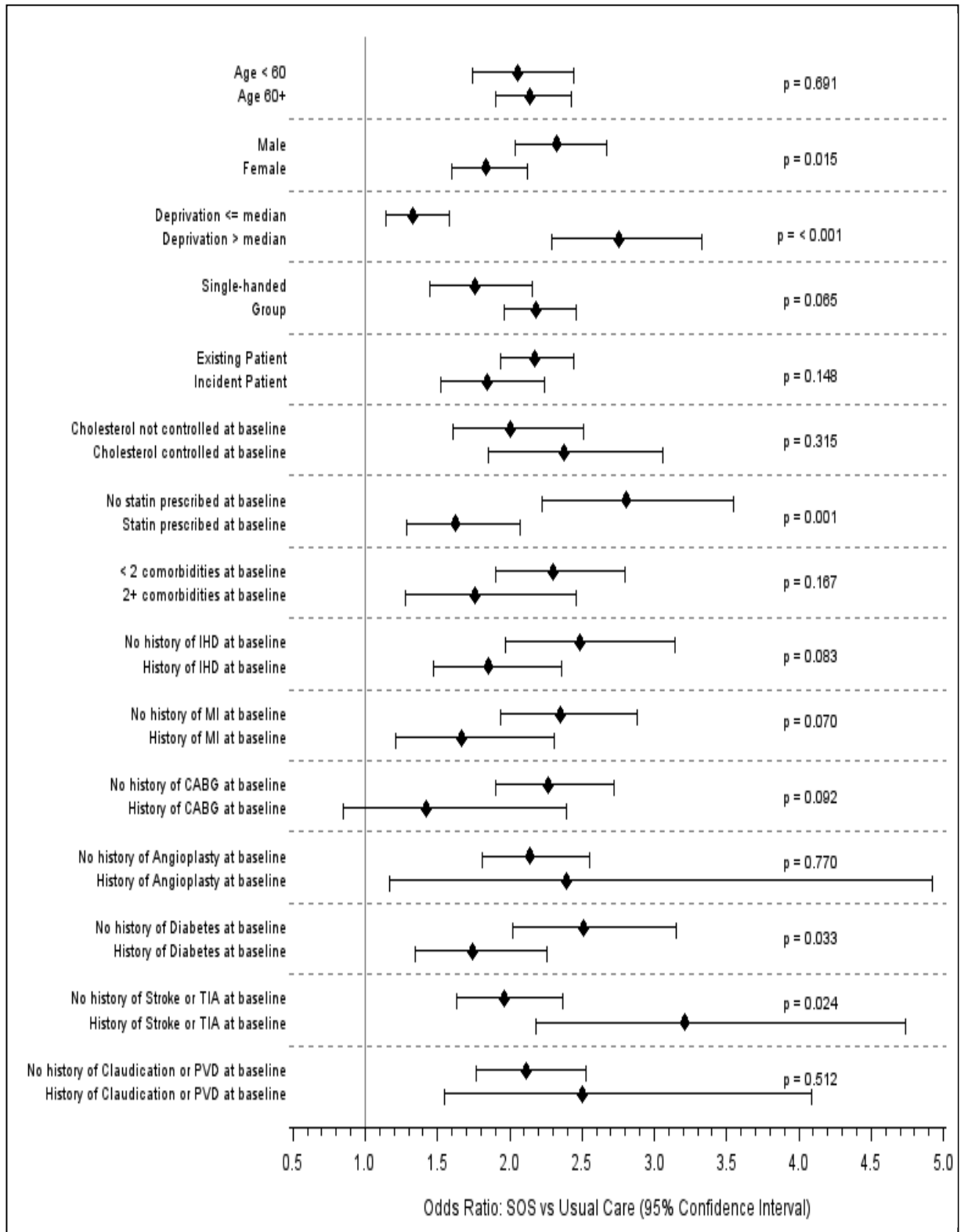


Figure 5.5 Subgroup analyses of secondary outcome: prescribing of simvastatin

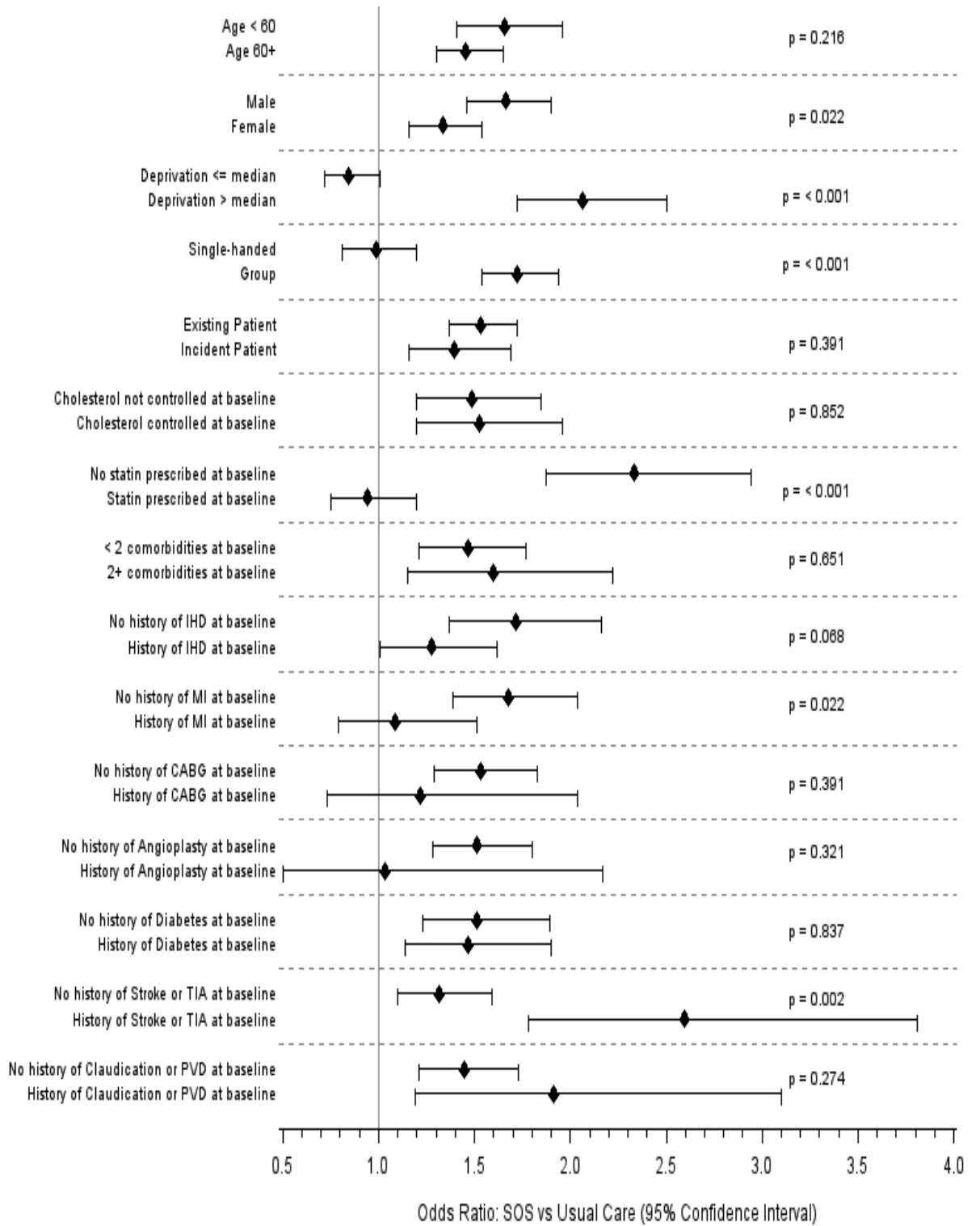


Figure 5.6 Subgroup analyses of secondary outcome: prescribing of any statin

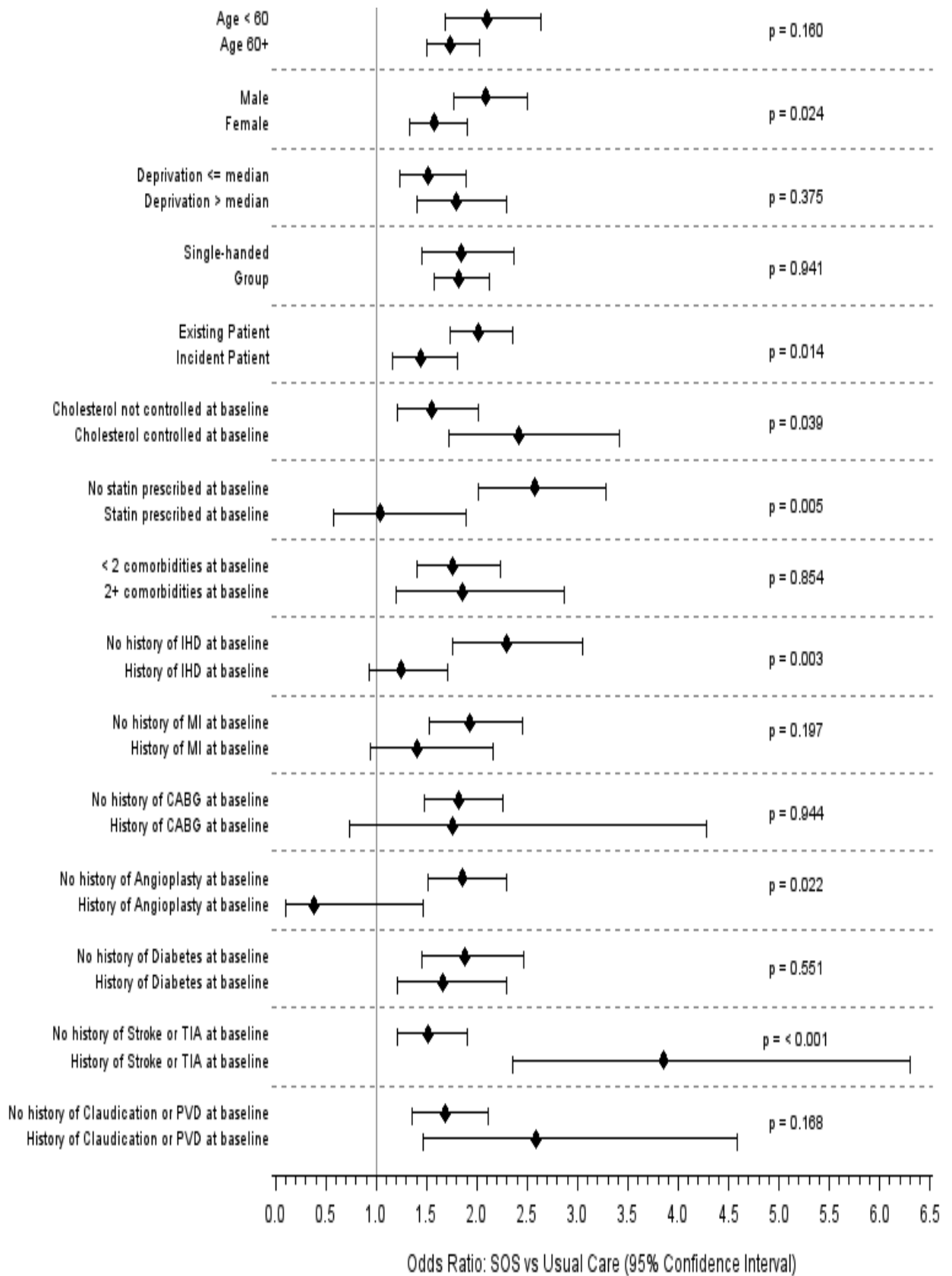


Figure 5.7 Subgroup analyses of secondary outcome: prescribing of Simvastatin 40mg and cholesterol tested

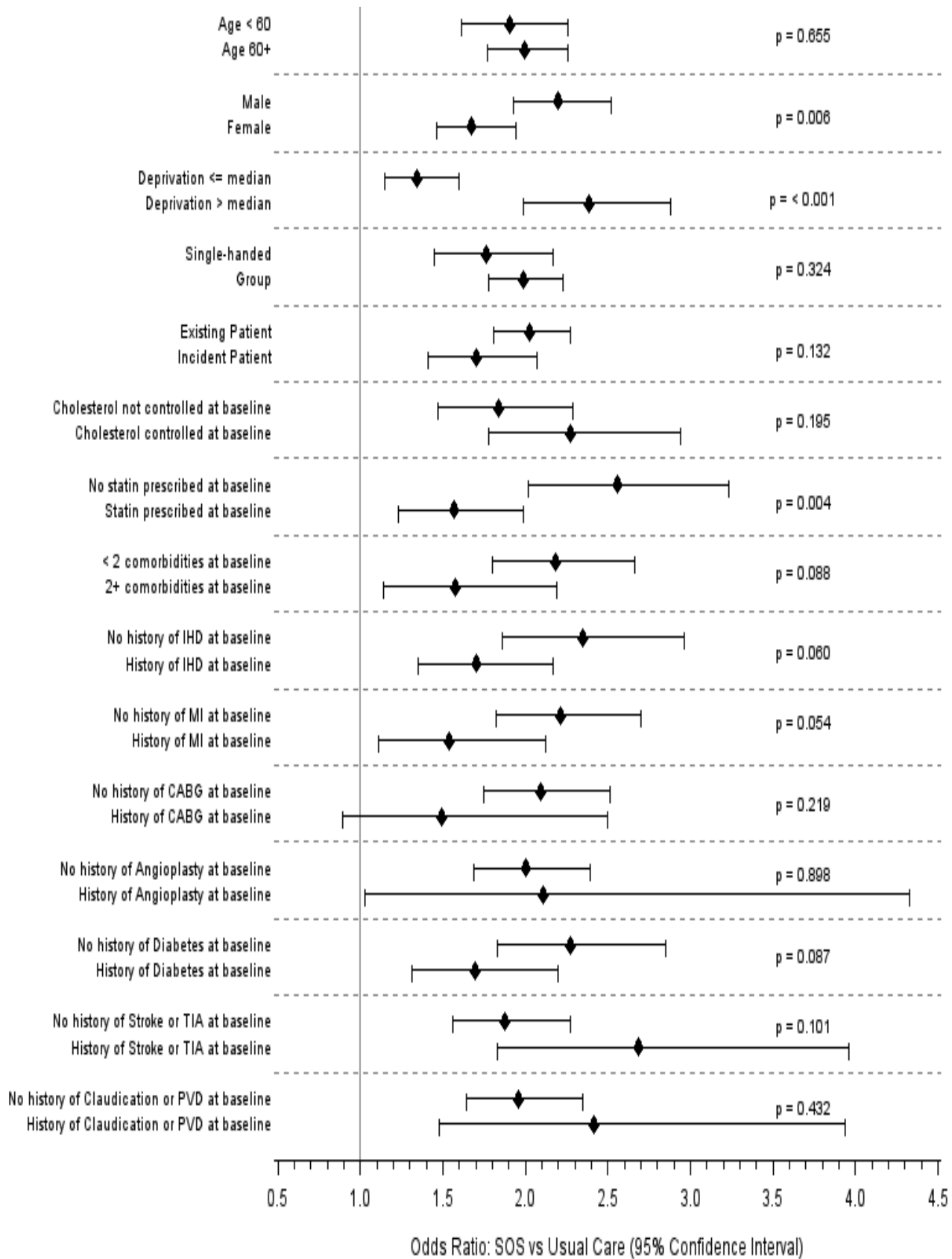
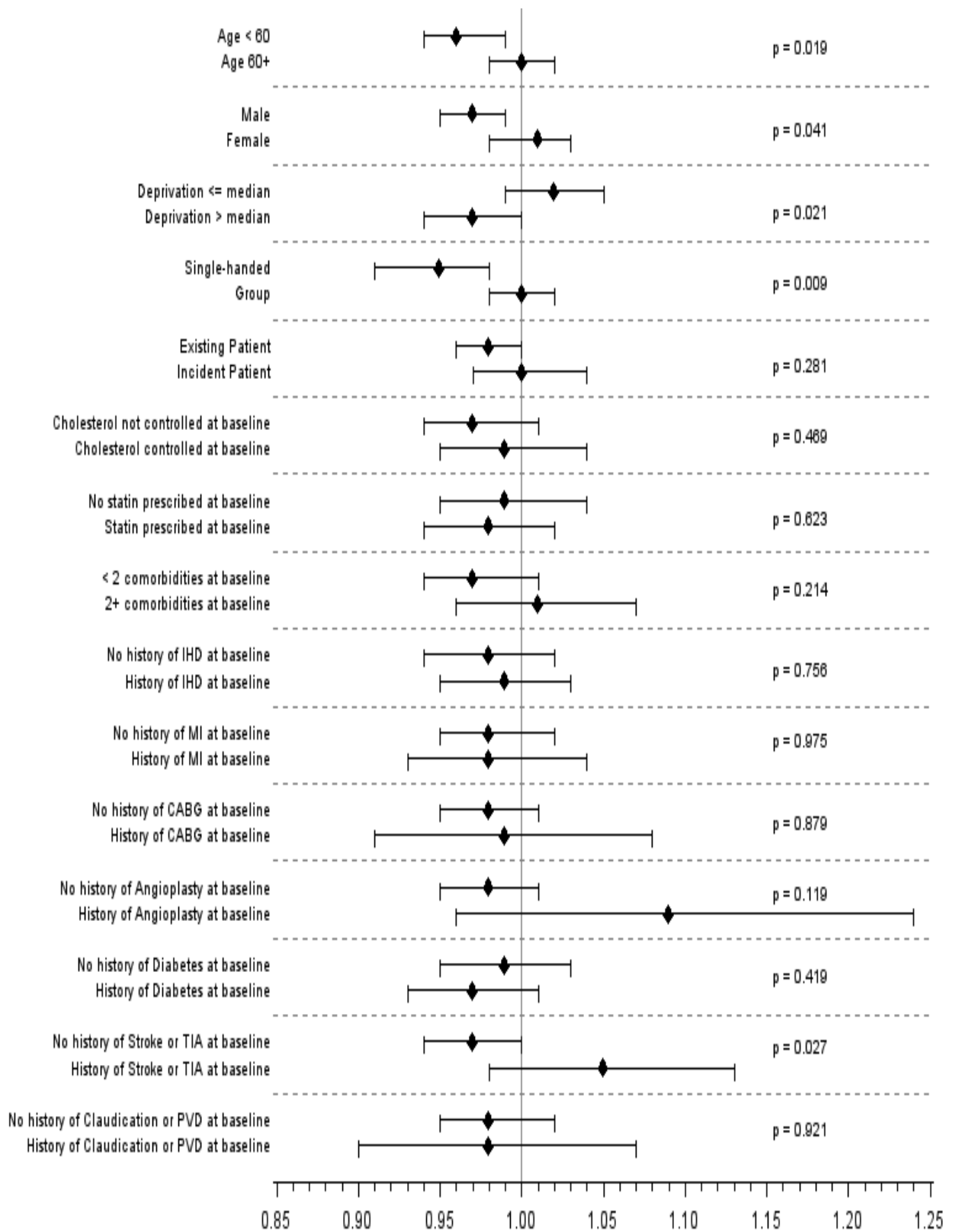


Figure 5.8 Subgroup analyses of secondary outcome: cholesterol levels of patients prescribed Simvastatin 40mg[§]



§ Point estimates to left of 1 represent favourable effect of SOS intervention

Ratio: SOS vs Usual Care (95% Confidence Interval)

Figure 5.9 Subgroup analyses of secondary outcome: cholesterol levels tested (all patients)

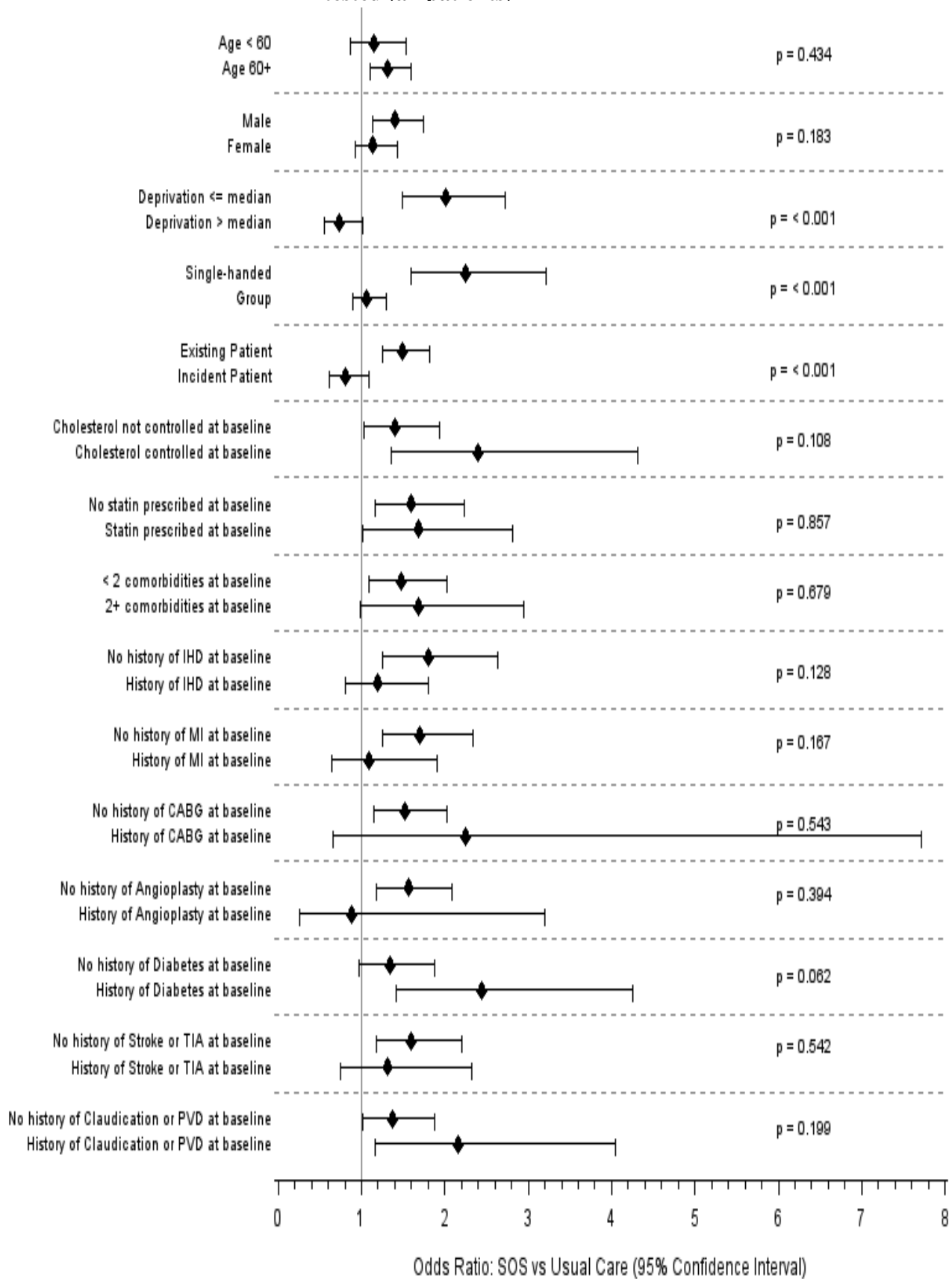


Figure 5.10 Subgroup analyses of secondary outcome: cholesterol levels controlled

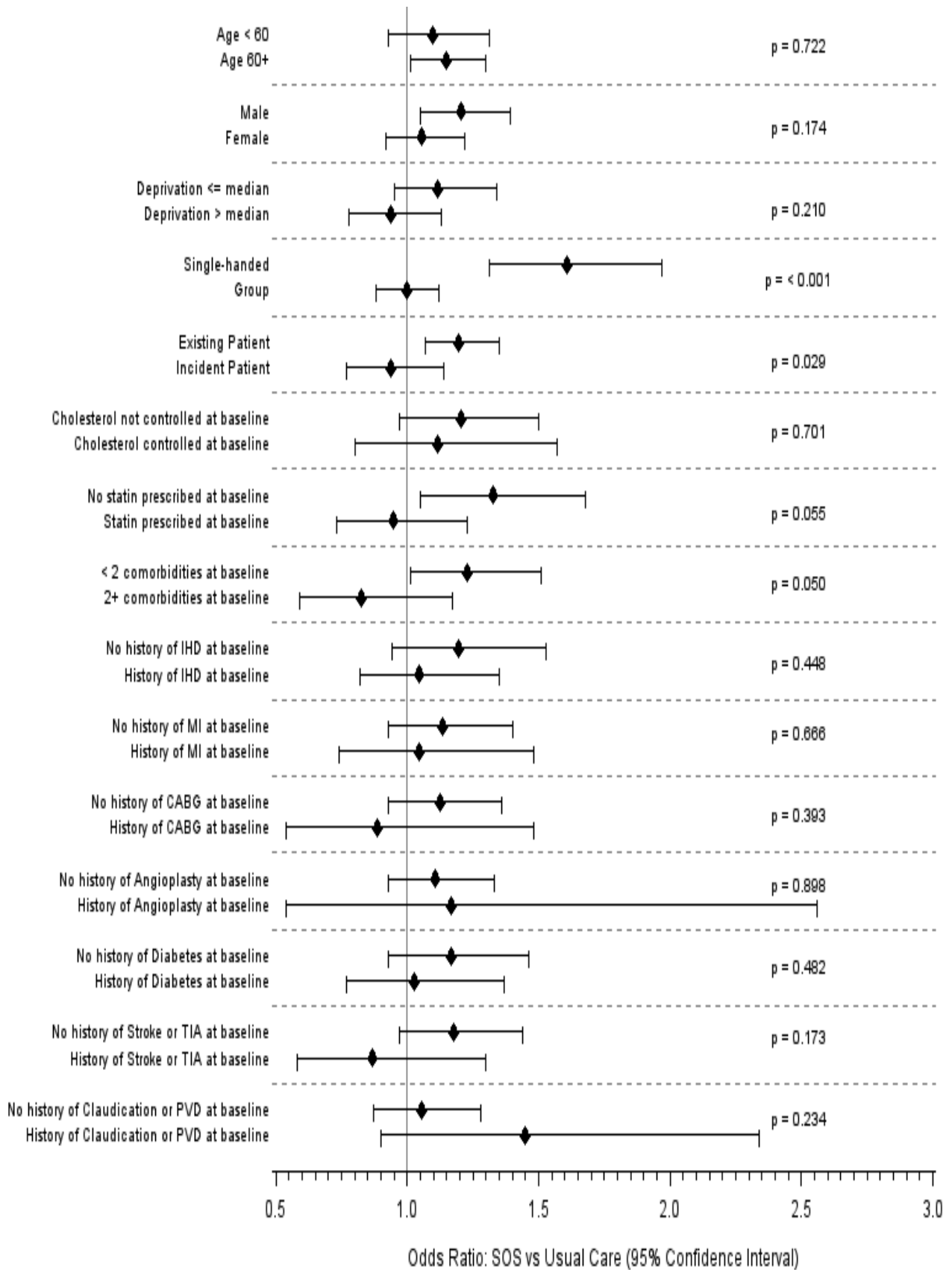
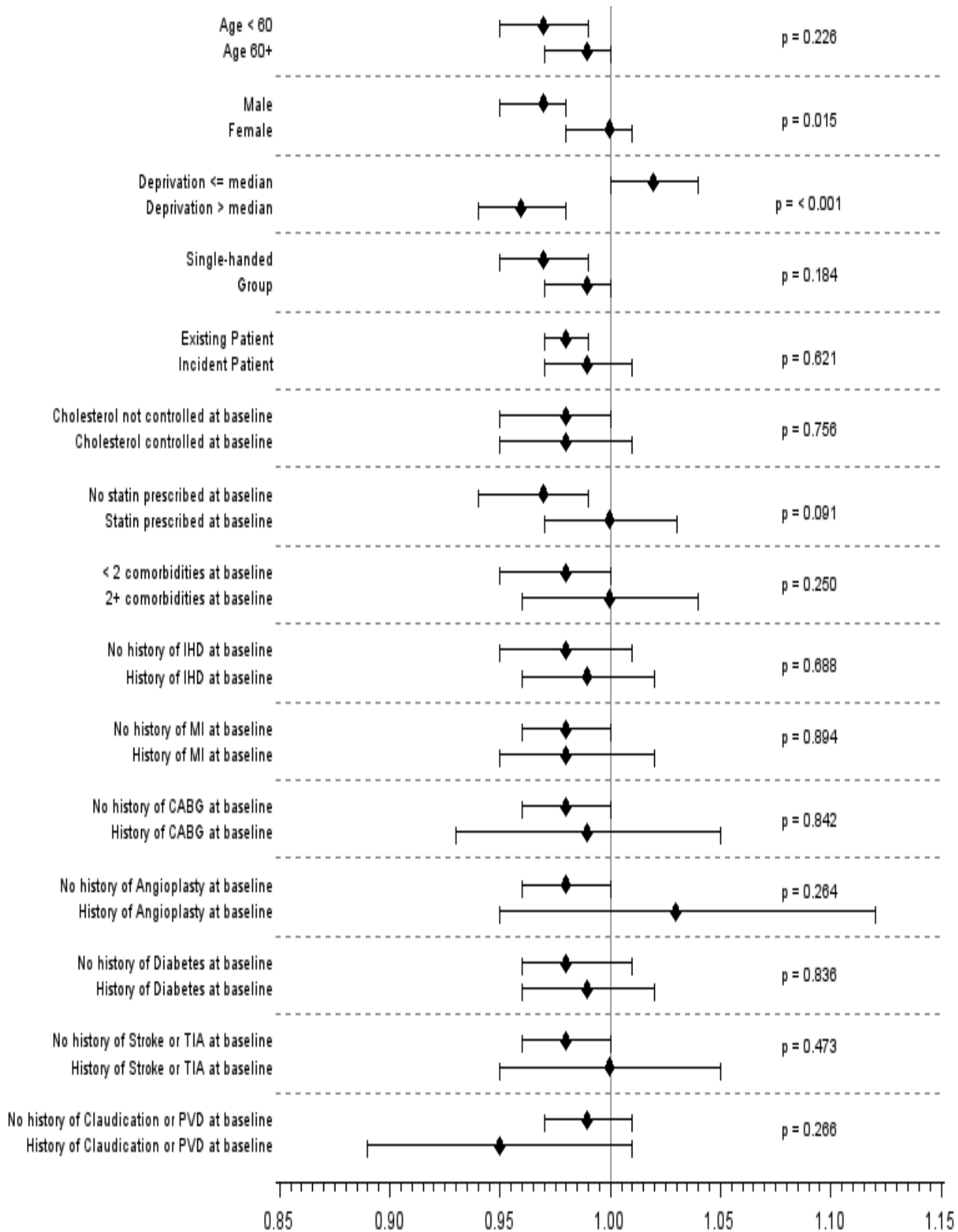


Figure 5.11 Subgroup analyses of Secondary outcome: Geometric mean cholesterol[§]



§ Point estimates to left of 1 represent favourable effect of SOS intervention

Ratio: SOS vs Usual Care (95% Confidence Interval)

5.4 Safety outcomes

A post-hoc analysis was conducted in order to determine if there was any significant imbalance in the time to occurrence of new vascular events (adverse events) in the SOS group compared with the UC group at a mean of 2.5 years follow up. Time to event analysis was used to test for differences between the intervention group and UC. Follow up duration varied between pairs, ranging from 2.2 – 2.8 years, but events were assessed during the same period within each pair of practices. Within pairs of practices, it was defined as the start date of the earliest baseline data collection until the end date of the last data collection at follow up or date of event if sooner (patients experiencing an event within this period were censored). If no events had occurred, the same date was used for follow up of the SOS and UC allocated practice within each pair. Cox proportional hazards models were fitted to the data; the model compared the rate at which patients first experienced any of the pre-specified vascular events, adjusting for pairing and treatment group. Hazard ratios were used to describe the difference between intervention and UC groups.

As described in Figure 5.1, we were able to ascertain the impact of the SOS intervention on the development of new vascular events in those patients who were tracked from baseline to follow up using their CHI number (n = 1911). Table 5.7 shows the percentage of each group who have had a vascular event. Researchers did not scrutinise eligible patient records in the assessment of safety outcomes. Instead, data was collected using a remote computer search linking patients by CHI number. While more efficient, this process was not validated and endpoint detection not confirmed in the usual way, through an adjudicating panel of experts. Only one significant difference was shown: time to occurrence of first presentation of diabetes SOS: 4 (0.4%) as compared with UC: 19 (2.3%). hazard ratio: 0.14; 95% Confidence interval 0.05 – 0.43; $p < 0.001$). Each hazard ratio was characterised by a wide confidence interval, reflecting considerable uncertainty about the point estimate, due to the low number of events within each diagnostic category.

Table 5.7 Comparison of adverse (vascular) events at follow up

Event	UC N=833	SOS N=1078	Hazard Ratio SOS vs. UC	95% Confidence Interval	p-value
Diabetes	19 (2.3%)	4 (0.4%)	0.14	(0.05, 0.43)	< 0.001
CHD	6 (0.7%)	3 (0.3%)	0.29	(0.07, 1.17)	0.081
Stroke	1 (0.1%)	6 (0.6%)	3.40	(0.40, 28.56)	0.260
CABG / Angiography	3 (0.4%)	3 (0.3%)	0.58	(0.12, 2.96)	0.517
Angina	1 (0.1%)	4 (0.4%)	4.10	(0.38, 44.70)	0.247
TIA	1 (0.1%)	1 (0.1%)	0.84	(0.05, 13.64)	0.904
MI	1 (0.1%)	2 (0.2%)	0.76	(0.07, 8.52)	0.826
PVD	0 (0.0%)	2 (0.2%)	NA		
Stroke/TIA/PVD	2 (0.2%)	9 (0.8%)	2.92	(0.62, 13.67)	0.174
CHD/CABG/Angiography/Angina/MI	10 (1.2%)	11 (1.0%)	0.67	(0.28, 1.62)	0.373
Any vascular event	29 (3.5%)	24 (2.2%)	0.55	(0.31, 0.97)	0.039

A total of 324 events of any type (vascular or non vascular) occurred in 215 of the 1911 patients who were tracked from baseline to follow up by virtue of their being identifiable by the remote, centralised data linking system. Only 53 / 324 of these were vascular as defined by the eligibility criteria of the study. Overall there was a lower incidence of events in the SOS arm. Improvements in statin prescribing and cholesterol control (and cholesterol levels) observed at follow up in the SOS practices may have influenced these, but this is a hypothesis requiring further testing in a sufficiently powered study. It is reassuring that the direction of the effect is in favour of the intervention.

5.5 Summary of results

Patients in practices exposed to the SOS intervention had statistically significant improvements ($p < 0.001$) in the primary outcome, and the following secondary outcomes: Prescribing of simvastatin; Prescribing of simvastatin 40mg; Prescribing of any statin at any dose; Prescribing of simvastatin 40mg and cholesterol tested since baseline.

The following secondary outcomes showed the SOS intervention to be more effective than UC, reaching the pre-specified significance level of $p \leq 0.05$: Cholesterol levels tested since baseline; Mean cholesterol levels (all patients) and Cholesterol controlled. The difference (in favour of the SOS intervention) noted in the secondary outcome: Cholesterol levels of patients prescribed simvastatin 40mg, did not reach statistical significance ($p = 0.221$).

While the intervention demonstrated improvements in these outcomes, the relative scale of the improvements differed considerably, depending on the outcome, and compared with baseline findings. For example, at baseline, the overall proportion of patients (with or without a statin) with controlled cholesterol was 38.6% (Appendix VII). This increased over time in the UC arm practices, to 63.6% of patients while the SOS intervention resulted in an increase to 69.5% of patients. This improvement reached the a-priori level of statistical significance (OR 1.11; 95% CI 1.00 – 1.23; $p = 0.046$. Table 5.6).

However, when the impact of SOS intervention on statin prescribing is considered, the effect was greater. For example, at baseline, 41.5% of patients were prescribed a statin (Table 4.5, obtained by averaging the proportion in SOS and UC prescribed a statin) and this increased to 86.9% in patients from SOS practices and 74.9% in UC practices (OR 1.82; 95% CI 1.60 – 2.06; $p < 0.001$. Table 5.6).

Further, when the change in prescribing of the target statin at the target dose is included in the outcome measure, the magnitude of the improvement in SOS is greater still. For example, the primary outcome of 'prescribed simvastatin 40mg and cholesterol controlled' reached 44.9% in SOS arm practices compared with 27.9% in the UC practices. The odds ratio in this case was 1.79 (95% CI 1.61 – 1.98; $p < 0.001$). At baseline, this measure was 9.9% (Table 4.6).

Therefore the extent to which the intervention increased the proportion of patients receiving Simvastatin 40mg with their cholesterol controlled was greater than the extent to which it increased measures of cholesterol control. The impact of SOS on all outcomes was mediated by the key intervention introduced by the pharmacists: prescription of Simvastatin 40mg for eligible patients. It is likely that the intervention achieved a statistically significant difference as a result of more patients receiving Simvastatin 40mg and more patients taking this prescription after initiation during the study and more patients within this target group attending their practice for cholesterol checks (without which, cholesterol remains unknown).

The intervention was effective for patients who were eligible and known to the practice at baseline, and for those who became eligible during the period of the intervention. However, of those patients linked from baseline to follow up, the intervention effect did not reach statistical significance for the subgroups with a CABG and those with more than 2 vascular diagnoses.

Characteristics of non participants from SOS and UC arms of the study were balanced. However, non participants' characteristics (demographics, qualifying diagnoses, cholesterol

and statin prescribing) differed from those of patients who were included at follow up. The reason for these differences is unclear, and requires further investigation.

An unintended but potentially important effect of the SOS intervention was to reduce the range of values for each of the outcomes studied, such that practices in the SOS arm showed higher values for the lower limits, compared with UC practices. The SOS intervention arm practices did not achieve higher values for each outcome; a ceiling effect was noted in each case. Subgroups showing persistently positive outcomes included males, patients from more socioeconomically deprived practices, patients known to the practices at baseline, those without a statin at baseline and patients with fewer vascular diagnoses.

There was no increase in vascular adverse events, evaluated through the appearance of new onset vascular diagnoses between 2.2 and 2.8 years after randomisation, in the subgroup of patients linked from baseline to follow up.

The clinical significance of these and other, untested effects arising from the SOS intervention remains to be confirmed, but these data prove the hypothesis that pharmacist led SOS intervention impacts favourably on a number of pragmatic, prescribing and surrogate clinical outcomes, across a wide range of practices and patient subgroups, up to 2.2 years post randomisation.

Chapter 6

Discussion

6.1 Overview

The continuing need for high-quality, unbiased physician education regarding drug therapies was recently reiterated by one of the researchers involved in the original academic detailing studies (Avorn 1983, 2011).

Throughout this thesis, the view has been that unbiased education is important but insufficient to reach patients in greatest need of support, and insufficient in itself, to sustain a change in prescribing practice. Therefore, in addition to education, practical, “hands on” help was provided by pharmacists to practices, for patients.

This chapter provides a discussion of the trial context, key findings, strengths, weaknesses, and potential reasons why the SOS intervention was successful, in comparison with other studies.

6.2 Trial context and summary of recent literature on pharmacist prescribing support

The SOS intervention involved close collaboration with GPs, nurses, practice staff and secondary care specialists. Some have described this type of multifaceted model as a ‘Complex intervention’ (MRC 2011), others have labelled it a ‘Collaborative model of care’ (Foy 2010; Unutzer 2002; Katon 2010). Because of the difficulty in accessing primary care physicians in some countries, the rising cost of secondary care and variation in the uptake of clinical evidence, greater use of collaborative models of care involving pharmacists has been widely advocated. The extended role of the pharmacist has been encouraged by governments in several countries including the UK (Medicine Use Reviews), USA (Medication Therapy Management), Australia (Comprehensive Home medicines review) and Canada (pharmacists have prescribing rights in Alberta, British Columbia and Quebec). It is therefore likely that pharmacists will continue to support prescribing and disease management, but the lack of evidence demonstrating added value in terms of morbidity / mortality outcomes may be a limiting factor in the widespread rollout of pharmacist led prescribing support in general.

In most cases, a direct patient facing model of support is advocated e.g. face to face medication review involving the pharmacist and the patient. This approach, if it is collaborative, is known to improve prescribing in line with guidelines of disease management and safety (Mackie 1999, Krska 2001, Zermansky 2001, Hanlon 1996, Furniss 2000, Sykes 1996, McGuire 1996). However, meta-analyses suggest a dearth of empirical evidence for benefit in terms of morbidity/mortality endpoints (Holland 2007, Royal 2006, Chisholm-Burns 2010).

The SOS trial was not powered to detect such endpoints but did include cholesterol lowering and cholesterol control as a secondary outcome. The link between cholesterol lowering

(control) and improved outcomes is strong and consistent across many robust studies: it is possible but less convincing to extrapolate these results into expected patient benefit.

The lack of evidence of clinical benefit from stand alone trials involving pharmacists' collaborative models of care may have spurred the recent increase in the number of methodologically robust studies with longer follow up. Since the end of the literature review period (February 2004), several studies have involved pharmacists, aiming to improve prescribing. These studies have included the testing of collaborative interventions (in which specialist trained pharmacists are employed) in primary care. Fihn (2011) tested the effectiveness of a pharmacist and specialist nurse collaborating to improve guideline implementation for patients with stable angina. Improvement of statin prescribing formed part of this, but no additional effect was found on a range of 'hard' endpoints. To date, collaborative care interventions involving pharmacists have not been shown to improve clinical outcomes in IHD or vascular disease.

Tests of the processes and outcomes of treatment for patients with depression, and diabetes have shown benefit (Unutzer 2002, Katon 2010). Meta-analysis of small trials, suggesting that the inclusion of a specialist pharmacist in collaborative, multidisciplinary team based care of patients with heart failure reduces hospitalisations (Koshman 2008). The use of specialist pharmacists in these and most other trials may reduce the generalisability of the findings and limit implementation potential. In contrast, a non specialist, pharmacist-led model of collaborative medication review in primary care, recently gave a neutral result (Lowrie 2011).

Soorapan tested the effect of pharmacist medication review intervention on type 2 diabetics in 2002 and found improvements in blood pressure but not HbA1c (Soorapan 2002). Mehuys updated this work by providing evidence, from a cluster randomised controlled trial, of the effectiveness of community pharmacists consulting with diabetic patients in Belgium (Mehuys 2011). Pharmacists met with patients monthly, delivering an intervention that comprised advice rather than recommendations for medicine changes. Their intervention appeared to be intensive (evidenced by the number of educational elements covered during consultations, although the duration of each contact was not given) and repeated up to six times in six months. They were able to show a statistically significant reduction in fasting plasma glucose, and HbA1c. The former remained reduced after 18 months while HbA1c had returned to pre-intervention levels by that time. Of note and of particular relevance to the findings from the SOS study, was the authors' observation that the reductions in fasting plasma glucose and HbA1c were mainly attributable to those in the intervention group who had received changes to their hypoglycaemic agents during the period of intervention. The intervention did not include changes to medicines and the pharmacists did not initiate these changes; general practitioners introduced the changes. This suggests that the effectiveness of their intervention was mediated at least in part, through GPs' changes to patients' medicines. The authors also noted (as we have) the relatively greater effect in those patients who had more to gain (poor glycaemic control at baseline). They recommended longer term follow up of pharmacist-led intervention, and (after acknowledging the likely impact of GP- mediated changes) stressed the importance of formal collaboration with GPs and the need to build prescribing change into the pharmacists' intervention.

In 2010, Villeneuve published a study demonstrating a neutral effect on cholesterol control, when community pharmacists teamed with physicians in Canada (Villeneuve 2010). Their intervention comprised advice on dietary measures to reduce cholesterol, and included

repeated patient contact which is thought to play an important role in achieving change (Dolan Mullen 1985). In their collaborative agreement, doctors were responsible for prescribing of lipid lowering therapy which is known to have a more rapid and powerful effect on cholesterol lowering compared with advice on dietary intervention. At follow up, patients in the intervention group were less likely to receive high potency lipid lowering agents, which offset the impact of pharmacists' counselling intervention and produced a neutral result.

Taken together with Mehuys' findings, it might be concluded that outcomes would have improved if the pharmacists had direct responsibility for initiation and up-titration of lipid lowering agents. Other studies have shown that pharmacists were able to adjust doses autonomously and produce statistically significant improvements in cholesterol targets, through direct patient interaction (Geber 2002, Cording 2002; Till 2003; Straka 2005; Rehring 2006).

More recently, Carter (2010) described the design of their ongoing multicentre cluster randomised controlled trial of pharmacist-physician collaborative blood pressure management with 5 year follow up. Carter reiterated the underlying aim shared by all prescribing support models and related research: "to implement models that work, overcome provider and health system barriers, and sustain the effect of interventions so that they can eventually be scaled up for broader use" (Carter 2010).

These recent studies re-state the need to demonstrate effectiveness in the short and long term, from pharmacist-led prescribing support. The studies appear to have improved internal and external validity, compared with previous research. However, overall, the quality of medication therapy management studies (and therefore the usefulness of their findings) shows room for improvement. For example, a recent review of randomised controlled medication therapy management trials (Kucukarslan 2011) applied internal validity criteria as recommended by Chalmers (1981), to assess trial quality. The review found only eight studies (from a possible 1795 published before 2009) meeting Chalmers' quality inclusion criteria. While the review focussed only on medication therapy management (most of which were led by pharmacists) as a model of prescribing support, the low number of valid trials highlights the need to conduct methodologically robust research if results are to be assumed as due to the interventions under investigation rather than misinterpreted due to confounding, bias or chance. In addition, none of the eight trials included follow up of longer than 12 months.

Meta analysis and systematic reviews are common, but publication bias may lead to meta analyses including more positive than neutral or negative findings. For example, a recent systematic review and meta-analysis of North American pharmacists' impact as team members on patient care, found favourable effects across many therapeutic and safety outcomes (Chisholm-Burns 2010). However, unlike Kucukarslan, the study by Chisholm-Burns failed to describe how they assessed the quality of their included studies. They included several studies of questionable methodological rigour (many of which had been rejected previously in Kucukarslan's analysis), leaving their conclusions open to criticism. Chisholm-Burns included the results from 298 studies compared with Kucukarslan's eight studies.

Across a wide range of settings, the studies described above underscore the potential for pharmacists' interventions to improve public health. To date, the following three features appear important, in combination, and were therefore incorporated into the SOS model:

1. Collaboration with existing care providers (general practitioners);
2. Repeated intervention;
3. Intensive intervention.

However, that there is no definitive evidence of clinical benefit over the long term, indicates the medication review model (or the studies to date), have limitations. The medication review model, in which the pharmacist consults directly with the patient then recommends changes to the GP, may not be the best model to influence GP prescribing over the long term. GPs may revert back to pre-intervention habits after the intervention is withdrawn, and this may lead to benefits being lost. However this has not been tested. The principle seems to apply to patients: after showing a reduction in heart failure hospitalisations, Murray found a rapid return to pre-intervention levels of hospitalisation in their study when pharmacist-led adherence support for patients with heart failure was withdrawn (Murray 2007).

Translating lessons from previous work into the SOS intervention

The model of prescribing support described and tested in this thesis attempts to achieve change and sustain it, by bringing pharmacists into an educational and organisational support role, within practices, collaborating fully with GPs, nurses and other practice staff. It incorporates theoretical behavioural change principles e.g. repetition and reinforcement of the main message, practical support for initial stages of change (Armstrong 1996, Bradley 1992, Oxman 1995, Dolan Mullen 1985). Core components of the SOS intervention include collaboration with existing providers of medication therapy management (GPs), repeated contacts and intensive support. All of which increase the chances of achieving a more sustained effect.

6.3 Strengths of the study

In 2002, the Cochrane collaboration reviewed trials of educational outreach, and made recommendations. These included describing interventions adequately, designing research more appropriately and analysing findings appropriately e.g. by considering the impact of clustering. Longer follow up was recommended, together with the selection of more useful outcomes (clinical or surrogate clinical e.g. HbA1c, Cholesterol) (O'Brien 2002). In planning and delivering the SOS intervention and study, we attempted to address these recommendations.

6.3.1 Complex intervention development

The SOS intervention was piloted and designed in accordance with the recommendations made by the Medical Research Council in 2000 and in 2011. Evidence points towards the increased likelihood of interventions working effectively, and studies being methodologically more robust, if MRC guidance is followed. Pilot testing was extensive, involving 5 different pharmacists working in 5 different practices, over a 1 year period. Pilot work enabled evaluation of the feasibility, acceptability, estimation of sample size and power. It also led to a consensus on the preferred components of the intervention, from pharmacist and general practitioner perspectives. A key strength of the study was the number of pharmacists who

delivered it: involvement of 11 different pharmacists leads to improved reproducibility of the intervention, and compared favourably with previous outreach research (Chapter 2). Another key feature was each pharmacist being able to adhere to the core parts of the intervention described in Chapter 3.

While intensive, the intervention did not overburden practices (or pharmacists) and was acceptable to 14 from 15 practices who agreed to receive it. Informal feedback on the model from practices to pharmacists and pharmacists to the study team was continuous, because the pharmacists communicated freely with GPs, nurses and other practice staff throughout their time in the practice.

6.3.2 Design

The SOS study was designed and is reported in line with recommendations for cluster randomised trials (Campbell 2004, MacLennan 2003). The unit of randomisation, allocation and intervention was the practice, as recommended for educational outreach trials in primary care. Following the recommended guidance is likely to lead to easier interpretation of the results, on dissemination, because the key features of the trial will be systematically described, in an accepted order and in sufficient detail to enable critical appraisal.

A stepped wedge (block randomisation) design (Brown 2006) offered an alternative methodological approach, but this was not practical because of the duration of the SOS intervention, and therefore, potentially even longer delays between study initiation and completion.

For the first time in a study of outreach, the pharmacists had full access to all relevant medical information held in the practice. This contrasts with previous work which has focussed on community pharmacists or specialists, working remotely, accessing anonymised prescribing trends.

The maximum duration of follow up previously described in this type of research was 12 months (Pearson 2003). Our median follow up was 20 months, ranging from 17 to 26 months, which is longer than previous studies of this type or medication review type interventions, excepting the recent HOOPS (Lowrie 2011). Longer follow up enables more accurate determination of the impact on clinical outcomes if the results are favourable. Persistence of the intervention effect after the intervention finished was therefore evident up to 16 months in some practices (the intervention lasted 12 months). Practice level simvastatin 40mg prescribing data up to 6 years post intervention showed a 'washover' effect in SOS arm practices (Appendix XVI), which breaks new ground in relation to effect duration, although this is outwith the controlled circumstances of the SOS trial and therefore less reliable.

Reduction of non formulary prescribing (in the case of Statins, the non-formulary choices at the time of the intervention were Rosuvastatin and Ezetimibe) is often the target of prescribing support models. The SOS model appears to have had a marked effect on reducing non-formulary prescribing, compared with UC practices judging by the trend shown beyond the designated follow up period (Appendix XVII).

Our process for selection of practices for inclusion in the trial was random, the aim being to recruit a representative sample to maximise external validity. This contrasts with most previous outreach trials, which have selected healthcare professionals on the basis of their capacity to benefit from the intervention on offer. While their approach to recruitment increases the likelihood of a positive result, ours maximises opportunities for transferability (Thomson 2005, Oxman 1995). There were few differences between participating and non-participating practices at baseline, indicating representativeness of practices, due to a successful, randomised process of practice enrolment (Lowrie, Morrison, McConnachie 2010). It involved following up those who had received an invitation, until an answer had been obtained. The desired effect was to reduce the chances of non participation by invited, busy or research-wary practices, ensuring generalisability of the practice sample. The study involved 15 single handed practices and the intervention, through improving outcomes in single handed practices, is likely to have improved QoF points in the domains covered by cholesterol control. Both factors are unusual because of the finding that smaller Scottish practices appeared less likely to participate in research and achieve fewer clinical or non-clinical Quality and Outcomes Framework points in the period 2002 to 2006 (Mackay 2010).

Key patient level variables at baseline and follow up were comparable to other statin trials and surveys, reinforcing external validity (Chapter 4). In particular, the large number of patients with data reported at baseline (4040) and follow up (7586) gives the results considerable weight.

Our sample size (practices and patients) was greater than anticipated, which perhaps improved our chances of finding a positive result, but also helped to minimise any remaining variability.

We controlled for confounding by pairing practices of similar baseline characteristics then stratifying, as recommended for cluster randomised trials involving few clusters (Donner 2000). Baseline data was collected before randomisation to minimise bias. Outcomes were assessed at the same time (relative to randomisation) in both members of each pair of practices, and by blinded, independent researchers. No interpretation was involved in the collection of outcome data. Transcription errors were a possibility, although the risk was minimised by the two researchers working together across 29 practices at follow up, which enabled cross checking for accuracy and completeness.

We randomly allocated practices to the SOS intervention or UC while maintaining blinding. Blinding is desirable because it minimises the chances of performance and detection bias. However, we could not ensure the 'quadruple blinding' approach described by Chalmers (1981), because practices were notified of their allocation in writing. Performance bias was therefore possible through UC practices trying harder to achieve the outcomes for which their SOS group counterparts received support. Further, participating doctors and other practice staff were not made aware of the ongoing results of the trial. Patients remained blinded to allocation throughout the study, because there was no requirement for written consent at patient level (Chapter 3).

All analyses were checked by an independent statistician, blinded to allocation, from the Robertson Centre for Biostatistics. We are confident that outcomes were due to the intervention, rather than any dissimilarity at baseline.

To date, assessment of the impact of outreach visits has focussed on markers of healthcare professional behaviour change e.g. the quality and quantity of prescribing or referrals. The SOS trial is the first to show benefit on cholesterol control and cholesterol levels, in the context of a randomised controlled trial.

Within the time period of the SOS trial, we were unable to evaluate any potential effect on hospitalisation, or mortality because the study was not powered to do so and this did not form part of the protocol. However, this may be followed up through a post hoc analysis, on completion of this thesis, alongside an economic evaluation.

6.4 Weaknesses of the study

Pre-intervention distribution of five variables of potential prognostic importance (cholesterol recorded, statin prescribing, statin prescribing at optimal dose, number of vascular co-morbidities and proportion of patients with angina/ischaemic heart disease) was disproportionate between the SOS and UC arms of the study. These imbalances may have been due to the small number of clusters however, they were not expected to have biased our findings for three reasons:

1. Their distribution acted against the intervention effect;
2. Cholesterol related measures (levels and extent of control between arms) were balanced;
3. Simvastatin (optimal dose) prescribing was balanced.

If the baseline imbalances were thought to influence the results, use of a regression model adjusted for these variables might be an alternative approach to analysis e.g. use of a stepwise selection to create a multivariate model.

Only practices from Greater Glasgow Health Board were considered in this study, and the intervention was delivered at practice level. The success of the intervention was therefore highly conditional, depending on the payment system and priorities at that time. Generalisability to other healthcare systems may therefore be questionable, particularly those with different primary care systems.

In common with other interactive educational outreach interventions tested in a controlled trial, participants allocated to the control group could not be blinded to their treatment allocation. This created two possible effects. The first is the 'Hawthorne effect' (Chapter 2, Section 4.6) which may have increased the statin prescribing of the control group as a result of an awareness of prescribing practices being under external scrutiny. The second effect is additive and may also have acted against the intervention: involvement in the study led to baseline data collection in each practice, by a pharmacist identifying a cross section of eligible patients and collecting relevant datum. Practices in each group had full access to this information, which remained in practices throughout the study. This information provided control group practices with a starting point for targeting eligible patients for statins and therefore, is likely to have improved outcomes in the control group beyond levels achieved by practices not participating in the study. These factors, together with the strong contextual influence of the QoF and the dissemination in December 2003 of the GG&C Cholesterol guideline, are likely to have led to the observed improvements in the UC practices. The extent

of improvement in UC arm practices between baseline and follow up was considerable: Appendix VII shows 36.8% of patients had cholesterol controlled in 2003 at baseline, while Table 5.6 shows 69.5% of patients in SOS and 63.6% in UC practices had controlled cholesterol at follow up in 2005/6.

This interpretation highlights a weakness of the overall research in not generating accompanying qualitative research to enhance our understanding of the reasons why the SOS intervention worked and to characterise the context for practices and patients in GG&C at that time.

6.4.1 Delays in reporting

There were significant delays in the completion and reporting of the SOS study. This perhaps represents a weakness of the study planning process. Reasons for the delay include having to rely on 11 pharmacists (at baseline) and two researchers (at follow up) for data collection. Therefore these phases lasted longer than expected. This led to significant delays between the start (2002) and finish date (2009; when follow up data collection was complete). Another reason for the delay in reporting was due to the time spent summarising and analysing the large data set generated by 7586 patients and multiple secondary outcomes and subgroups.

In the interim, statin prescribing is likely to improve and this will tend to reduce the impact of the SOS intervention and reduce the need to implement our findings. For example, Kumar recently reported the prescribing of statins for patients with vascular disease in the USA had reached 84% (Kumar 2009). Their survey included 19,007 patients, making it the largest survey of statin prescribing to date. This level of achievement is very close to that shown in the SOS study at follow up (prescribing of any statin at any dose in the SOS group was 86.9% compared with 74.9% in the UC group. Kumar did not collect data on doses or cholesterol levels. Due to the time delay between study completion and reporting, the SOS intervention may have become less useful for most general practices, but more useful for general practices with more modest levels of statin prescribing and dosing. The delay in reporting will be turned to our advantage by extending the follow up period.

Delays also increase the likelihood of similar research reaching publication, superseding our work. However, between 2003 and 2010, there does not appear to have been any published randomised controlled trials or other scientific investigations focussing on general practice based pharmacists improving statin prescribing and cholesterol control for patients with vascular disease, through educational outreach-type approaches. The RaPP trial was comparable in some ways. Starting in 2002, the authors aimed to achieve better prescribing of antihypertensives (mainly thiazides) and statins for a primary prevention cohort (Fretheim 2003; 2006) through group based educational outreach delivered by pharmacists. Improved outcomes were limited to thiazide prescribing, with no effect on statins or cholesterol control.

6.4.2 Attrition

When data are collected over at least two time periods, most studies have some degree of dropout of patients or in this case, clusters and patients. Attrition may introduce bias if the patients or practices dropping out are systematically different from those remaining in the study. The SOS study was different in that more patients were included at follow up, than were included at baseline (Figures 5.1 and 5.2). This included larger numbers of incident

patients in both arms (SOS: 999 / 4234 (23%) and UC: 927 / 3352 (28%). However, we have not yet compared the characteristics of different subgroups.

However, we had no reason to believe that these limitations biased the results. Baseline characteristics (Tables 4.2, 4.4, 4.5 and 4.6), suggested groups were well balanced at baseline. Outcomes (and subgroup analyses) strongly favoured the intervention and were consistently positive for the group identified at follow up (n = 7586; Table 5.2) and the subgroups: eligible at baseline (n = 5660; Table 5.4) and eligible after baseline (n = 1926; Table 5.4). Of the 5660 patients who were eligible at baseline, 2619 (SOS: 1491 / 2373 (63%) and UC: 1128 / 1667 (67%). Table 5.2 and Figure 5.1) were linked from baseline to follow up, and outcomes were also positive for this subgroup.

The proportions of patients who could not be linked from baseline to follow up because of missing data e.g. CHI, was similar in both study arms: SOS: 880 / 2373 (37%) and UC: 541 / 1667 (32%). However, some of the characteristics of these non-participants differed from the characteristics of those patients who were linked from baseline to follow up (Tables 5.2.1 to 5.2.5). In particular, non participants appeared to be older and more likely to be female compared with those who were identified at baseline and followed through the study. Thus the possibility remains that the intervention effect is untested in this subgroup of patients. While subgroup analyses of the primary and secondary outcomes showed improvement in males and females, Section 5.3.1.3 describes some evidence, from subgroup analyses, of a preferential effect of the intervention in males compared with females. The intervention did not appear to be of reduced effectiveness in older age groups as defined by the threshold: < 60 years compared with ≥ 60 years. It is therefore possible that a more detailed analysis of the effect of age using smaller increments may show a different result.

However, the size of the differences in age (3.2 years), gender (6.4%) and other variables e.g. qualifying diagnoses between participants and non participants (Table 5.2.4) while statistically significant, may not be of clinical importance. One difference does stand out: non participants were less likely to have diabetes than participants. This requires further exploration and may be attributable to there being fewer non participants from practices serving predominantly South Asian communities where the occurrence of diabetes was found to be greater at baseline (Section 4.3.2).

We found no statistically significant difference in mortality in the 82% (1168/1421) of non participants who had sufficient data to enable determination of their status. Approximately one third of non participants died prematurely before the end of the study. As the proportions of non participants dying prematurely before the end of the study was balanced between SOS and UC groups, this is unlikely to have biased the results.

Previous research into the effectiveness of various outreach models has focussed only on GP or family physician's prescribing or test ordering activities, without describing the characteristics of patients or whether they were known to the GPs / physicians at baseline. Compared to previous research of this type, we had a more detailed description of patients and differentiated between prevalent (known at baseline, n = 5660) and incident (n = 1926). Evaluation of the impact of the SOS intervention on patients tracked from baseline to follow up (as is the norm in individually randomised trials) was therefore another novel aspect of our study.

6.4.3 Therapeutic topic

The intervention focussed on a relatively restricted area of therapeutics, and the underlying reasons for disparities between clinical practice and systematically developed guidelines are known to vary from one clinical problem to another. Our pilot work, training of pharmacists and the SOS model were tailored to the specific and temporal needs of practices and statin prescribing. Further pilot work and a different training programme may therefore be required, to test the model on a different topic. However, we have provided prima facie evidence that the method might work, when applied to another therapeutic area.

By only targeting changes in statin prescribing behaviour for patients with vascular disease, the intervention may be regarded as having relevance only for a relatively small (high risk) group of patients. This is not a problem per se, but may become difficult to sustain if an economic model shows the approach not to be cost effective.

6.4.4 Design considerations

Importance of sample size calculations

Sample size calculations are a means of estimating the required number of participants in each arm of a randomised controlled trial, in order that a clinically important difference is detectable, when the occurrence of the most important outcome in the intervention group is compared with the control group.

If a study is too small, it will not be able to answer the question posed. Sample size calculations are important because they guard against over or under recruitment of participants, both of which may impact on ethical, cost and risk implications, depending on the type of trial. The SOS study was a pragmatic (practical, effectiveness or management) trial conducted using NHS resources, nested in routine care through the delivery of pharmacist led prescribing support to improve adherence with established GG&C statin prescribing guidance. The intervention was introduced in addition to usual care; practices and patients were not denied any service as a result of the study. Re-organisation of the delivery of a NHS funded pharmacist support service together with standardisation of an outreach/organisational support intervention minimised any ethical concerns and additional costs. Senior management within NHS GG&C were supportive of the trial proceeding using NHS resources within routine service delivery to inform decision making in relation to the effectiveness of pharmacist led prescribing support in primary care.

The sample size depends on the type I and II error rate and the effect size of the intervention. The sample size goes down inversely as the square of the effect size. In the case of cluster randomised controlled trials, the sample size calculation takes account of a measure of the correlation between individuals within a cluster and the size of the cluster.

In the case of the SOS study, the sample size calculation (based on pilot work conducted in 2002) focussed on the effect size of the outcome: the proportion of patients with CHD who had cholesterol controlled. This outcome was chosen because of the finding (following an extensive literature review) that pharmacist led interventions had not previously shown any improvement in surrogate clinical outcomes, and surrogate clinical outcomes are more useful markers of effect to the NHS and patients, compared with changes in prescribing. To derive empirical evidence of improvement in cholesterol control through a practice level intervention would therefore break new ground and represent a valuable outcome for patients and NHS GG&C. Analysis of pilot work subsequently showed that the intervention generated a measurable improvement in cholesterol control. The study sample size and power calculation were based on this outcome. At that time, one of the secondary outcomes was the proportion of patients with controlled cholesterol, prescribed simvastatin 40mg.

However, during this period, there was an increasing focus (instigated by the director of finance in NHS GG&C and communicated through to pharmacist prescribing support teams) on prescribing cost containment. Statin prescribing and costs were increasing and some of the increase was due to more expensive statins e.g. Atorvastatin 10mg costed £18.03 for 28 days compared with £1.32 for Simvastatin 40mg for 28 days (BNF 2009). The statin prescribing / cholesterol guideline for secondary prevention was introduced to improve the quality of prescribing (encouraging more eligible patients to receive a statin) and to minimise the costs associated with statin prescribing by encouraging the prescribing of Simvastatin 40mg. The guideline adopted the eligibility criteria of the Heart Protection Study, superseding the

previous eligibility criteria used in our pilot work: coronary heart disease. Following discussion with finance and management colleagues, it was therefore decided to revise the main target of the study to reflect the prevailing ethos of cost containment, while retaining the focus on cholesterol lowering. Therefore the primary outcome became the proportion of patients with vascular disease who were prescribed Simvastatin 40mg with controlled cholesterol.

For pragmatic reasons, the study therefore had a sample size and power calculation based on a secondary outcome. This raised the possibility of the study being over or under powered to detect the primary outcome.

The power of the study can be re-calculated using follow up data:

- assuming 7586 patients in total (3793 per arm) in 29 practices ($7586/29 = 261$ per practice).
- design effect (D) = $1 + 0.05 (261 - 1) = 14$ (*Section 3.2.4*)
- effective sample size is $3793 / 14 = 271$ patients per group

Therefore the study had 94% power to detect the difference in the rate of the primary outcome of 88% in SOS versus 76% in UC, and 98% power to detect 44.9% in SOS compared with 27.9% in UC.

Both outcomes (primary and secondary) were binary. The power of each was sufficient to detect a difference of a similar magnitude: 88% versus 76% in the original calculation compared with 44.9% versus 27.9% in the calculation shown above.

The persistence shown during the recruitment process may have contributed to one practice dropping out. This is because the practice may not have had sufficient opportunity to appreciate the intensity and duration of the SOS intervention. Our invitation process comprised systematic follow up through personal visits, letters, faxes and telephone calls until confirmation of consent or non participation had been received from each practice. In some cases, the practice received a letter, fax, phone call and visit to discuss the programme. This enthusiastic approach led to the recruitment of three practices which had not previously participated in any research. Of these three practices, one disbanded prior to the date of randomisation, one dropped out and one remained in the study.

We did not formally evaluate GP, practice nurse, practice staff, patients' or pharmacists' views. We do know from practice staff in the SOS arm that there was no negative feedback from the patients who did receive some form of communication or changed prescription. GPs and nurses appeared appreciative of the pharmacists' input; all 35 GPs and 21 nurses willingly participated in the study although 1 GP and a practice nurse (from the same practice) dropped out. Patient views of outreach services delivered to GPs have not, as far as we are aware, been reported. Literature on GPs' views of academic outreach visits is limited to one short report that indicates a preference by GPs for other GPs to deliver these interventions (Young 2003).

At baseline, using available data, we found patients' characteristics were comparable to those described in landmark, placebo controlled trials from the same period. However we did not collect additional data e.g. the number and type of non-vascular co-morbidities, weight, height, previous hospitalisations or smoking status. Physiological variables e.g. blood pressure and eGFR would enable better characterisation of the population, and thereby enable other researchers to compare and contrast our findings more widely.

At baseline (and therefore randomisation) there were significant differences between the SOS and UC arm practices in the following covariates: proportion of patients with Angina/Ischaemic Heart Disease (significantly greater in SOS intervention practices), vascular co-morbidities (greater in SOS practices) and cholesterol recorded (lower in SOS practices). Together these data indicated SOS allocated practices had a greater burden of patients eligible for statins, but less information on which their prescribing decisions could be based (fewer patients with available cholesterol levels at baseline). Also, proportions in SOS intervention practices without a statin were higher and prescribing of optimal doses of statins was lower. Both these imbalances suggest practices in the SOS arm had a larger gap to bridge to improve on the levels noted in UC. In turn, this may have led to a need for proportionately more effort to achieve a given target statin prescribing and cholesterol control. Therefore, the baseline imbalances did not appear to bias the results in favour of the intervention.

Critically, the groups were balanced in relation to the primary outcome: simvastatin prescribed and cholesterol controlled at baseline.

Measurement of adverse events is an important consideration in the clinical trial setting but less so for complex interventions health services research. We chose to evaluate new diagnoses of vascular disease because this study was primarily about the impact of SOS intervention rather than the impact of statins per se. Vascular diagnoses (limited to those included in the eligibility criteria) were collected through electronic record linkage of those patients who had CHI recorded and were identifiable at baseline and follow up. Electronic searching and reporting is likely to have been more accurate, complete and efficient because of the lack of outcome interpretation required by researchers. However, in this case, the process involved remote searching of participating general practices' databases using a central server, of unknown accuracy and completeness. Therefore, that SOS and UC arms were found to be comparable in relation to adverse events, cannot be taken as conclusive. The low number of events in each group led to wide confidence intervals, indicating considerable uncertainty around the results. The proportion and time to occurrence of new diabetes diagnoses, where the intervention showed superiority over UC, is likely to have driven the significant difference in the overall safety analysis of all events. There was no scientific rationale for there to be delayed onset of new diabetes in the SOS arm of the study. One recent report noted the opposite: a possible link between increased risk of diabetes and statin use, in women (Vos 2011). Subgroup analyses for the presence or absence of diabetes in the primary or secondary outcomes confirmed there to be no significant difference in the impact from the SOS intervention.

Post-hoc analyses to detect adverse effects arising from complex interventions may be useful to generate a hypothesis rather than confirm or refuting a prior hypothesis. In exploratory trials e.g. those involving new medicines, safety analyses are important because of the need to confirm safety in use in a heterogeneous group of patients. However some observers regard safety analyses in complex intervention trials as unnecessary (John Norrie, personal

communication) because of the difficulty attributing causation of potentially unrelated outcomes, following the application of a multifaceted intervention in the context of a complex system with many interacting factors.

The effect size of our study was larger than expected from pilot work, which led to our decision to conduct a post hoc analysis because of the possibility that systematic application of the statin/cholesterol guideline in a heterogeneous population led to an effect not previously considered. The SOS study was not powered to detect any differences in safety outcomes and the analysis of vascular events at follow up did not form part of the original protocol. In addition, the method used to collect the number and type of events further limited the usefulness of these results:

1. The number of patients identified through this analysis (215 / 1911 (11%) over 8 months is considerably greater than the expected approximate rate of 2% over 8 months (30% over 10 years). Practice level verification of these events and their associated coding did not take place. Without these in process quality controls, the results cannot be regarded as conclusive.
2. The method used to identify the occurrence of new vascular events had not been previously tested or validated therefore was of unknown specificity and sensitivity.
3. The period (between 2 and 2.8 years) chosen for the evaluation of vascular events was chosen for pragmatic reasons, rather than any a-priori decision underpinned by an evidence base relating to when adverse events of this nature may occur.
4. Collection of adverse events was limited to new presentations of diagnoses comprising the eligibility criteria for Simvastatin 40mg. No other relevant outcomes were sought. These might have included ascertaining the level of reported side effects from simvastatin. However, during the HPS (which included 20,536 UK adults), these were already known to be rare: less than 0.5% in the case of alanine aminotransferase elevated more than four times the normal range; less than 0.2% in the case of creatinine kinase elevated more than 10 times the normal range and less than 0.1% for rhabdomyolysis. We had no reason to believe there was a need to evaluate the incidence of these or other side effects from a commonly used, licensed medicine.

Patient level non-vascular mortality was not sought as part of the post-hoc analysis for two reasons:

1. This was not requested in the original ethics committee application
2. Resources were not available to enable unique identification of mortality using Information Services Division record linkage or other verification processes.
3. Non-vascular mortality rates in a heterogeneous population receiving Simvastatin 40mg is already established. The HPS showed any non-vascular causes of death in the intervention group reached 5.3% (547 / 10269) with 5.6% (570 / 10267) in the placebo group; death rate ratio 0.95; 95% confidence interval: 0.85 – 1.07; $p = 0.4$)

For these reasons, the results of the SOS post hoc analysis cannot be taken to imply causation. If the diabetes result in the safety analysis is taken as a signal of a protective effect from simvastatin 40mg, further investigation of this finding in the context of an adequately powered study is required.

6.5 Key findings

At baseline in our sample, half of those eligible were treated with a statin and half of those treated were uncontrolled. The 'rule of halves' (Wilber 1972) was also evident at baseline for other measures of statin prescribing and cholesterol control. The prescribing of the recommended statin (simvastatin 40mg) for eligible patients was considerably less than 50% at baseline: 8.9% in SOS practices (211/2373) and 9.4% in UC practices (157/1667) (Tables 4.5 and 4.6).

We found that a new, high intensity, collaborative SOS model of pharmacist-led prescribing support delivered over 1 year, involving a combination of personalised educational outreach and organisational support delivered to unselected general practices, improved statin prescribing and cholesterol levels, of patients at highest risk of suffering a vascular event.

Patients with confirmed evidence of vascular disease in practices receiving the SOS intervention were almost twice as likely to have simvastatin 40mg prescribed with controlled cholesterol. Most subgroups benefited, but the following benefited more than their opposites: males, those who were living in areas of greater socioeconomic deprivation and patients diagnosed with vascular disease before the start of the intervention.

Patients from practices receiving the SOS intervention had increased prescribing of target dose simvastatin or any other Statin. Patients were more likely to have their cholesterol tested (in accordance with guidelines, when this was due), controlled (less than 5mmol/l) and have lower cholesterol levels.

The intervention effect was strong enough to show a statistically significant improvement across most outcomes, despite improvements in the processes of care of patients with vascular disease, financially incentivised from 2004 by the GMS QoF.

There were some statistically significant differences between patient non participants (who could not be followed up at the end of the study). Premature death is likely to have accounted for loss to follow up in one third of cases although mortality was comparable between SOS and UC as were all other baseline variables.

6.6 Interpretation

An average, 261 eligible patients with vascular disease were identified per practice, at follow up. Of patients from practices receiving the SOS intervention, 59% were prescribed simvastatin 40mg at follow up compared with 38% in the UC group. Therefore in SOS intervention practices, for every 100 eligible patients, 21 more were prescribed simvastatin, which approximates to the number needed to treat for 5 years, to prevent 1 event (heart attack, stroke or revascularisation (Appendix III). With 261 patients per practice and 14 practices receiving the SOS intervention, an estimated 35 events were prevented between 2005 and 2010, in the SOS allocated practices, with the following assumptions:

- Prescribing of simvastatin reached a plateau at the point of follow up data collection;
- Risk predictions from the Heart Protection Study applied to our sample (26% event rate without and 21% with simvastatin 40mg);
- Patients took at least 80% of their statin.

Pharmacists working collaboratively with practices supported an increase in simvastatin 40mg prescribing from 8.9% to 58.9% at follow up, while in UC practices, a considerable increase from 9.4% to 37.8% was noted, without pharmacists' support.

It is likely that as time passes, the margin for improvement from the SOS intervention will diminish, in line with the general improvement in uptake of incentivised prescribing through the 'pay for performance' system in the United Kingdom (Roland 2004, Campbell 2007). Crude estimates of the overall rise in prescribing of simvastatin (primary and secondary prevention) in the SOS intervention practices compared with UC beyond the period of the study is shown in Appendices XV and XVI, suggesting an increase over time, and also persistence of the effect of the intervention, at least six years later. The dramatic increase in simvastatin 40mg prescribing in the UC arm coincides with the introduction of the GMS QoF.

The model could be applied to improve the use of other guideline based therapies, where uptake is suboptimal; perhaps an area not covered by the GMS QoF e.g. the prescribing of guideline recommended beta blockers for patients with symptomatic heart failure due to left ventricular systolic dysfunction. However, it is difficult to predict whether practices would be sufficiently motivated to receive the support of the pharmacist without the additional prospect of (contractual) financial incentives for achieving higher rates of prescribing or dosing.

6.7 Key features of the intervention

The SOS intervention was delivered by 11 different pharmacists, but core components of the intervention were delivered as standard by all. These components were described in relation to setting, timing, duration, content, structure.

As with other complex interventions (O'Brien 2002; MRC 2000 and 2011), it is not clear which components were essential although access to patient level clinical and prescribing information was a pre-requisite. The following are likely to have been vital:

1. Prolonged, intensive prescribing support. This enabled relationship building, with associated trust, which led to agreement on prescribing recommendations. It also enabled the pharmacist to have sufficient time to carefully identify eligible patients and categorise them in relation to their required action e.g. needing cholesterol checked, or a prescription for simvastatin 40mg. Both male and female pharmacists delivered the intervention effectively in their allocated practices and there was no obvious link between the number of years or type of experience or possession of a postgraduate qualification and a successful outcome.
2. Identification of barriers to change (GP, nurse, practice, and to a certain extent, patient barriers). Pharmacists exchanged and shared different approaches to solving problems that were common between their colleagues in different practices. Organisational support is known to help overcome prescribing inertia (Nazareth 2002), and the additional capacity to deal with this, clearly helped overcome workload constraints.
3. Access to all practice based demographic, diagnostic and prescribing information.

4. Provision of the means to overcome (practice specific) organisational barriers e.g. creation of “free” slots in nurse or GP daily lists, so that eligible patients can appear for cholesterol tests or to receive a statin prescription;
5. Provision of individualised information. Tailored interventions are known to be powerful predictors of effectiveness (Hulscher 1998, Figueiras 2001). The SOS intervention was tailored to each practitioner and their practice circumstances.
6. Systematic follow up and updating of practice based patient records to ensure maximum uptake and minimum dropout.
7. The hard work and enthusiasm of the pharmacists delivering the intervention.

To drill down any further would require a prospective (cluster) randomised controlled trial of different components of the SOS intervention, accompanied by the views of practice staff on their perceptions of the strengths and weaknesses of the intervention.

6.8 Primary outcome

We chose a primary outcome combining simvastatin 40mg prescribing and cholesterol control, because this captured uptake of main prescribing message communicated to practices while including a measure of whether patients began taking simvastatin. It was therefore considered to be the most appropriate means of evaluating the impact of the intervention, while giving an indication of the real world consequences of improved prescribing (cholesterol lowering and control).

The effect size (OR 1.79; 95% CI 1.61 – 1.98) of the primary and many of the secondary outcomes was greater than previous educational outreach interventions or collaborative approaches to prescribing change (Bloom 2005).

The primary outcome effect was greater in males, patients from areas of greater socioeconomic deprivation and patients with fewer vascular co-morbidities. These findings were unexpected, particularly the greater impact on patients from practices in areas of greater deprivation, a finding which applied across all secondary outcomes and subgroups and merits further exploration, perhaps through examination of individual level deprivation scores. The greater effect on practices with higher average mSIMD becomes more striking when taken in context of the deprivation scores for practices across Scotland (Section 4.1.2). Most participating practices were within the 9th or 10th (most deprived) deciles, suggesting the intervention can improve outcomes in practices from the most deprived areas of Scotland. The intervention may provide a means of addressing the inverse care law (Hart 1971), particularly if the principles are applicable to other conditions e.g. supporting general practices in more deprived areas to increase the uptake of cardiovascular health check screening (O’Donnell 2009 internal report) This application has been tried with good results, since the findings of the SOS trial became clear (Lowrie 2010b internal report).

An important role of implementation research is to reduce the differential uptake of clinical evidence, because significant variation is likely to lead to inequities. A reduction in the range of each outcome was observed in the SOS arm practices. In each case this was due to the SOS intervention re-setting a higher (improved) minimum value. Together, this provides strong evidence that the SOS intervention effectively reduces between-practice variability in the minimum achievement in each of the outcomes studied, by re-setting the minimum level to a higher value. This is useful for patients in practices where the starting point is lower.

A comparison of the upper limits of the ranges achieved at follow up revealed minimal difference between SOS and UC practices. It indicates that practices not receiving the SOS intervention are able to achieve the targets achieved by pharmacists' support. Therefore if practices use their patient level demographic and prescribing information differently and have sufficient additional focussed time and effort then improvements of the scale introduced by the SOS intervention are possible. It is also likely that the proportionately greater effect of the SOS intervention in more deprived areas reflects the ability of the model to overcome the added difficulty usually experienced by these practices due to additional workload.

The similarity of the upper limits reached for each practice (SOS and UC) suggests a ceiling effect. It is possible that general practices have difficulty achieving levels beyond the thresholds indicated e.g. 93.6% of eligible patients prescribed a statin, or 69% of patients with cholesterol controlled. The consistency of this finding across most outcome measures perhaps suggests that factors outwith the control of the practice were at play in limiting scope for 100% achievement. Possibilities include the remaining eligible patients declining a statin (or an increase in dose), statin intolerance, some patients not being easy to engage. Reasons for poor engagement were encountered by pharmacists and practices in their course of systematically contacting eligible patients. They included patients who had moved house without informing the practice, housing block destroyed, relocated, not willing to cross boundaries between their home and the practice for territorial reasons or not able or willing to pay two different bus fares to attend an appointment in the practice during their work hours. Many of these findings were encountered again (confirming their validity) in 2010 during a separate programme of work focussing on improving practices' engagement with people from areas of socioeconomic deprivation in Glasgow (Lowrie 2010b internal report).

To achieve a greater extent of achievement in the primary outcome is perhaps unrealistic with the SOS model; further improvements may require more interventions directed towards patients e.g. for improvement of adherence. Outreach to patients' homes would undoubtedly help overcome subsequent barriers and this approach may be tested next. Variability in response to statins and lifestyle measures (diet and exercise, both of which influence cholesterol levels) are also possible explanations for the gap between the ceiling levels we observed and 100% achievement.

6.9 Subgroups and secondary outcomes

6.9.1 Gender

De Wilde (2003) found men were more likely than women to receive a statin, but the difference disappeared after adjustment for age and severity of ischaemic heart disease. Both sexes are known to benefit equally from statins (25% reduction in cardiovascular disease incidence), but women tend to be under represented in statin trials (Bartlett 2005). A meta-analysis of five major statin trials (4S, LIPID, CARE, AFCAPS/TexCAPS and WOSCOPS) found the risk reduction in major coronary events was similar between men and women (La Rosa 1999). In the HPS, a comparable reduction in events was demonstrated in males and females. There does not appear to be a clear report in the literature of the relationship between

statin prescribing and gender in primary care, but the clinical evidence overwhelmingly asserts statins should be offered to both males and females based on risk stratification.

Our findings are consistent with some reports of higher uptake of statin prescribing among men with ischaemic heart disease (13.3%) compared with women (8.2%) e.g. Majeed 2000, Reid 2002, but not others e.g. Bartlett 2005). A recent systematic review of primary care programmes to prevent cardiovascular disease found no evidence of gender inequalities in uptake (Pennant 2010).

There was no preferential targeting of males by pharmacists in the SOS intervention. This may suggest greater uptake of recommendations to start or up-titrate doses in males, or a greater number of males were identified as requiring improvements, or a combination of both. Alternatively, women may have declined more offers of improvement to their statin prescribing. Further work is needed to explore the reasons why the impact on males was greater than in females.

6.9.2 Age

Age differences were investigated as a subgroup because of the evidence that increasing age (in the range 55 to 84 years) has been shown to reduce the odds of receiving a statin (De Wilde 2003). This (erroneous) perception surfaced during some one to one discussions between GPs and pharmacists, when GPs raised concerns about the scope for the elderly to benefit from statins. Available evidence suggests that the benefit from statins is not attenuated with increasing age. Therefore pharmacists delivering the SOS intervention were made aware of this and asked to encourage prescribing according to level of risk rather than age, in line with the recommendations of a meta-analysis of five randomised controlled trials involving 30,817 participants (La Rosa 1999).

Differences in response according to age (we used a pragmatic distinction of 60 years or less compared with over 60 years) were not apparent in either the UC practices or SOS practices at follow up: proportions of patients in the UC and SOS arms achieving the primary outcome in each age band were similar. This finding applied to the subgroup analyses of primary and secondary outcomes. As with the other subgroups, a statistically significant increase was noted in SOS arm practices, in the proportion of patients achieving the primary and secondary outcomes. These findings suggest that the SOS intervention achieved improvements in prescribing in line with guidance on risk rather than age.

6.9.3 Existing versus newly diagnosed patients

The SOS intervention achieved a greater impact in the primary outcome and in the secondary outcome of 'cholesterol levels tested since baseline', for patients known to the practice at randomisation.

This result was expected: in SOS practices, pharmacists provided an updated, cleaned list of their eligible patients, using data collected at baseline. Implementation of the SOS intervention's key messages for new cases relied on the practice continuing to identify, call and recall eligible patients for statin initiation. Setup of these systems were encouraged by the

pharmacists but may have been less robust, more opportunistic and therefore less successful than the systematic approach to identification of all eligible patients at baseline. ‘Existing’ patients had been invited through letters and / or phone calls, or offered a statin opportunistically while attending for an unrelated, scheduled appointment.

However, the intervention was also effective for those patients who became eligible after baseline. One reason why the intervention effect persisted for the newly diagnosed cohort in the SOS arm practices compared with UC was possibly due to the pharmacists ensuring at least one named member of the practice assumed responsibility for following up statin prescribing and cholesterol checking for this group of patients. The result stresses the importance of providing practical support and helping practices to overcome what has been previously described as “organisational barriers”. The same explanation could be an explanation of why there appeared to be a continued effect on practices’ simvastatin 40mg prescribing (for all patients, primary and secondary prevention) beyond the period of the study (Appendix XVI). In some SOS arm practices, there was already a reasonably tight system for patient identification and call/recall. In these practices, the pharmacists’ intervention mainly focussed on educational rather than organisational support.

Subgroup analyses of the primary and several secondary outcomes e.g. cholesterol levels controlled and tested, prescribing of any statin, reinforced the finding that patients known at baseline fared better than those identified at some point afterwards. The most convincing evidence came from the outcome ‘cholesterol tested’ which is not surprising: one of the first tasks of the pharmacist in SOS arm practices was to identify those requiring cholesterol tests and systematically invite them to attend an appointment for a cholesterol test. Patients in this subgroup at baseline had a longer time to receive changes to their prescription, make an appointment at their practice and attend for a cholesterol test. Practices in the UC arm appeared less likely to have applied such rigorous approaches to call and recall for this focussed group of patients, resulting in less baseline-eligible patients attending for a cholesterol test.

6.9.4 Deprivation

The practice level mSIMD was used to measure deprivation and within those practices recruited, an arbitrary division made between higher and lower mSIMD. Patient level mSIMD is a more sensitive measure, and could be considered in further analyses.

There is conflicting evidence about whether deprivation status influences statin prescribing rates (Ward 2007, Reid 2002). In Glasgow, the extent and depth of deprivation is greater than most other areas in Western Europe and the incidence of Ischaemic Heart Disease and related disorders is greater than the rest of Scotland. Socioeconomic deprivation is known to increase the risk of developing ischaemic heart disease and worse outcomes are expected as a result. Under these circumstances, the SOS intervention may be of particular interest to practices and policymakers faced with addressing cardiovascular health inequalities.

In planning the SOS trial and providing training to pharmacists, we anticipated some additional efforts would be required to engage with patients from practices serving areas of greater deprivation, based on awareness of the problem from the published literature (Gardner 1999; Tod 2001) and our own observations. In these practices, or for patients in other practices

with a history of poor attendance, pharmacists expected to spend more time providing additional setup support to generate accurate lists of eligible patients and to expect additional difficulties e.g. missing phone numbers or frequently changed addresses. Our expectations were confirmed: with few exceptions, while working in these practices, pharmacists observed and informally reported less stringent call and recall arrangements than in practices serving patients from more affluent areas. In practices where systems were already in place, these tended to be less effective when confronted by patients who perhaps had countless more pressing priorities in their lives than to attend for an additional appointment in their practice. The Pharmacists were clear that their role was to ensure each eligible patient received an offer of an appointment or a statin.

Increased time spent by pharmacists identifying eligible patients and supporting the practice in their attempts to contact and re-contact patients, are likely to be key reasons for the noted improvement in outcomes. Another important reason was that pharmacists were able to scrutinise patient records for missing phone numbers and updated addresses, which were often 'hidden' in discharge notes from Accident and Emergency or NHS 24 consultations. Practice computer records were then updated accordingly. Using recent contact details, practice staff had a greater chance of contacting patients. Given the known difficulties experienced by smaller practices in more deprived areas in relation to attainment of organisational aspects of QoF (Wang 2006), the success of the SOS intervention provides a model of joint pharmacist-practice working that is capable of delivering improved statin prescribing and cholesterol control.

Because of the additional workload involved, it is unlikely that this support was received across all practices in the UC arm of the study. In practices serving more deprived areas, the pharmacists noticed a disproportionately greater number of patients receiving initiation or dose modification of statins opportunistically, during appointments for other purposes. The pharmacists therefore met with reception staff to explain the SOS intervention approach and this led to booking of double appointments for some eligible patients, when these patients had booked a single appointment for an acute problem. In some cases, when these patients arrived in the practice for collection of repeat prescriptions, reception staff referred them into the practice nurse who initiated simvastatin 40mg and agreed a repeat appointment for follow up cholesterol levels liver function tests, if indicated. It is possible that this concerted action led to the surprise finding of a higher proportion of patients from practices with higher mSIMD who had simvastatin 40mg, attending for cholesterol checks (Figure 5.7). It is possible that reduced practice nurse availability e.g. invited, non-participating practices, would have had more difficulty responding in this way.

The burden of ill health in poorer areas and the resulting increased demands on general practices is known to be associated with poorer access to care, reduced consultation times and lower patient enablement for psychosocial problems (Mercer 2007). Acknowledging the need to change this status quo, the results presented here suggest that pharmacist-led support can improve access to optimal dose statins, increase the likelihood of cholesterol control and reduce cholesterol levels among those in greatest need. Endpoints were maintained up to 2.2 years post intervention suggests a higher level of acceptability of changes to GPs and patients than has been shown previously in educational outreach interventions. It is possible that in supporting statin prescribing and cholesterol management to this degree, GPs in the most deprived practices had more time to focus on the psychological distress and other issues commonly presenting in consultations. More work is needed to confirm the latter.

6.9.5 Coronary Artery Bypass Graft

For most secondary outcomes, the subgroup of patients with CABG or angioplasty showed no significant improvement following delivery of the SOS intervention. However, confidence intervals were wide, indicating more uncertainty, due to lower numbers of patients.

Prescribing of statins for patients with CABG may have been optimal prior to application of the SOS intervention, leaving little room for improvement (Chap 5). De Wilde found a similar result in their survey of lipid lowering drugs in 142 general practices across England and Wales (De Wilde 2003). Patients who had a history of revascularisation were more likely to receive a statin than those with angina. Reasons for better prescribing of statins in this group were unclear from De Wilde's work and from our work. However, if the underlying socioeconomic gradient for access to CABG and angioplasty (Hippisley-Cox 2000) was operating, these patients may have had better communication skills and awareness of the need for statin treatment, both of which would be expected to increase the prescribing of statins. Alternatively, the influence of secondary care initiation of statins, post operatively, may have a role, or GPs knowing the increased risk of this cohort, introducing and up-titrating statins more readily than in patients with angina.

6.9.6 Cholesterol controlled at baseline

These subgroups were analysed because they gave an indication of whether one of the more contentious messages in the educational outreach programme was accepted: the need to introduce simvastatin 40mg for patients who already had controlled cholesterol.

The SOS intervention increased the proportion of patients in both groups prescribed simvastatin 40mg. There was no interaction between the groups indicating no significant preferential effect on one subgroup over another. Therefore compared to UC, pharmacists delivering the SOS intervention managed to convince GPs to modify either the choice of statin or dose, or both, in line with guideline advice, regardless of starting cholesterol level.

6.9.7 Practice type

At the design stage, we hypothesised that some Single Handed practices would have less success at initiating, and titrating statins or their methods of call/recall for cholesterol testing, would be less robust compared with Group practices. In keeping with this, Wang et al later confirmed that Scottish urban single handed practices had lower attainment of QoF organisational domain contract points (Wang 2006). Stratification removed the risk of this impacting on the results.

We found a statistically significant difference in the SOS intervention effect for prescribing of simvastatin, in favour of patients from Group practices. This indicates group practices (and their patients) were more likely to respond to the SOS intervention. However this pattern was not repeated across other secondary outcomes and the opposite was true for the outcome 'cholesterol levels of patients prescribed simvastatin 40mg' which was more improved in Single Handed practices than Group practices. Single Handed practices and their patients also

responded better than Group practices and their patients, in relation to attendance for cholesterol checks, which might have accounted for the higher proportions of patients in Single Handed practices with controlled cholesterol levels.

In the EBOR trial, community pharmacists visited general practices to encourage the uptake of prescribing guidelines (Nazareth 2002). Larger practices responded less than smaller practices, which is broadly similar to our findings.

It is possible that the observed shifts in Group practices were significantly less than those resulting from application of the SOS intervention in Single Handed practices because of a 'ceiling effect': patients in Group practices were already close to the upper limit. Attempts at further improvement might have followed a law of diminishing returns. By comparison, Single Handed practices, in having a lower starting point, had more room for improvement. On a pragmatic level, the same time was spent by pharmacists in Single Handed and Group practices, which suggests that Single Handed practice staff and patients received proportionately greater intensity and duration of input from the pharmacists, resulting in better outcomes.

Without a process evaluation running in parallel to the main trial, it was difficult to confirm the reasons for these observations. However, pharmacists delivering the SOS intervention in Single Handed practices consistently reported that the GPs were more appreciative of their help (the pharmacists did not report this level of positive feedback so often in Group practices). In some Single Handed practices, the support bordered on one to one outreach, one day per week for a year. In Single Handed practices, we found that GPs tended to have greater awareness of their patients and their histories together with that of their families. It is possible that patients from Single Handed practices, due to a stronger 'personal' relationship with their GP, were more likely to accept the GPs' advice and recommendations. Part of the greater effect size in smaller practices might be attributable to this. Our finding of improved outcomes in Single Handed practices indicates the usefulness of SOS as a mechanism for supporting organisational and educational quality improvement.

Greater Glasgow Health Board had the highest concentration of Scotland's ethnic minority population. (General Register Office for Scotland 2004). At the time of the study, diabetes prevalence in Glasgow was known to be higher in South Asians than in the indigenous white population (4.8% compared with 1.3%) (National Resource centre for Ethnic Minority Health/Public Health Institute for Scotland 2003). The problem was particularly severe for patients over 70 years where prevalence of type 2 diabetes was nearly 14 times higher than among those under 50 years (National Resource Centre for Ethnic Minority Health and The Scottish Diabetes Group 2004). In line with the results of the main study, outcomes were improved in two practices allocated to the SOS arm, serving patients within predominantly South Asian communities.

While South Asians represent a particularly high risk subgroup, there is evidence that the inverse care law applies: the use of services is less for Ethnic Minority groups (NHS Scotland. April 2002) with reduced access in cases where English is not the patient's first language (Free 1998). At the time of the SOS study, over half of Scotland's Local Health Care Co-operatives did not document the cultural or religious requirements of their patients and one fifth do not provide patients with access to interpreters (Diabetes in Minority ethnic groups in Scotland (National Resource Centre for Ethnic Minority Health and the Scottish Diabetes Group 2004)

There is some evidence that key medicines known to improve diabetes related outcomes are prescribed less frequently amongst Ethnic Minority patients (Patel 2002). Statins may be under-prescribed in minority ethnic patients (Ashworth 2006).

The intervention achieved a significant level of improvement in the prescribing of statins and cholesterol control, in a subgroup of minority ethnic patients from practices where the majority of patients and the GPs, were of South Asian origin. SOS has therefore managed to overcome the inverse care law as it relates to the narrow yet important area of statin prescribing for South Asians in primary care. This finding could be set in the wider context of health inequalities which can be shaped by inequalities in access, availability and quality of services or linguistic, cultural and gender barriers often embedded in clinical practice (Dans 2007).

6.9.8 Statin prescribing at baseline

Patients without statins at baseline were more than twice as likely as those without, to have achieved the primary outcome after the SOS intervention. Alternatively, this could be interpreted as SOS having a larger benefit for those patients with no statin at baseline because of a lower starting point, with a comparable final outcome being achieved in UC and SOS. Either way, this finding was anticipated because GPs in both UC and SOS were thought to be less likely to change stable patients' statins to simvastatin 40mg if the original prescription (choice of statin and dose) was well tolerated. However the impact of the SOS intervention in the group already prescribed a 'statin at baseline' was statistically significant, confirming the high level of acceptance of the main message to prescribe simvastatin 40mg in preference to other statins.

Together these findings are important because in most outreach / educational support studies to date, practices or healthcare professionals have been targeted for recruitment on the basis of their increased capacity to benefit from the intervention. The SOS intervention is therefore likely to be effective when applied to an unselected population of practices and patients, conditional on baseline prescribing and cholesterol levels being comparable to ours.

6.10 Cost minimisation

One of the key messages from the SOS intervention was the need to prescribe the least expensive statin with the greatest amount of clinical evidence of effectiveness and safety, at optimal dose. This approach was in the spirit of public interest detailing, to counter increasing use of more expensive medicines with no greater efficacy or safety profile e.g. Rosuvastatin or Ezetimibe, often driven by pharmaceutical industry or advocates within the NHS. The challenge of prescribing statins in line with the evidence yet managing to remain within prescribing budget in primary care is well known (Evans 2000). In prescribing more statins in SOS arm practices compared with UC, our results indicate prescribing costs will have increased as a result of the intervention. However, in each case, the intervention addressed unmet need; in view of the benefits of statins in reducing the risk of clinical events, and a full economic analysis is required to evaluate cost effectiveness from an NHS perspective.

6.11 Impact of SOS intervention on cholesterol

In primary care, there are several steps between prescribing a statin and achieving a lower cholesterol level. Statins need to be taken regularly for at least 2 – 3 months, to inhibit cholesterol synthesis to the point where a lower steady state plasma level is achieved. Each step is potentially subject to patient dropout or non adherence.

The SOS intervention arm practices had a greater proportion of patients with their cholesterol tested, controlled, and lower mean cholesterol levels. For those in whom it was tested, mean cholesterol decreased by approximately 0.1mmol/l as a result of the SOS intervention. In comparison with landmark statin trials e.g. HPS, our reduction is of the order of 10 times less but our participants differed from those recruited in HPS not least because there was no requirement for pre-trial demonstration of acceptable medication adherence. The clinical significance of better statin adherence was illustrated in the WOSCOPS trial: patients who took 75% or more of their Pravastatin reduced their risk of death from any cause by one third more than those who took less than 75% (LaRosa 2005) and, like the findings from the HPS, this effect was independent of cholesterol lowering.

The intervention did not include any attempt to improve adherence with statins, through direct patient interaction. It was therefore more difficult for the intervention to improve adherence, compared with improving Statin prescribing. However, cholesterol control was significantly improved in SOS arm practices. This is likely to result from the increased prescribing of statins in the SOS arm, the increased use of higher doses, more patients attending for cholesterol checks, or a combination of these factors. Further work is needed to confirm the precise cause, because the complex intervention affected all outcomes. Alternatively, other influences were involved e.g. a higher level of adherence by patients in the SOS arm practices perhaps in response to their practice contacting them and showing an interest in their prescribing and cholesterol.

Systematic bias is likely to have been minimised by the randomised enrolment of practices and the randomised controlled trial design.

Statin adherence is known to be poor in the community and improving adherence is known to be more difficult than improving statin prescribing. At one year, adherence to statins is estimated to be about 60% in patients with previous cardiovascular events (Colivicc 2007; Blackburn 2005; Jackevicius 2002). A recent study reported an unsuccessful pharmacist-led adherence support intervention for patients prescribed statins (Ma 2010). In their recommendations for further work, the authors suggested a stronger focus on influencing physicians to increase statin prescribing.

Other studies involving pharmacists aiming to reduce cholesterol levels have focussed on community pharmacists' activities. Most (including a meta-analysis by Machado in 2008) have shown some degree of improvement in cholesterol levels, albeit with pharmacists working directly with a small number of patients (Tsuyki 2004). The most recent report is from Canada, where a cluster randomised controlled trial tested the effectiveness of a collaborative care model involving community pharmacists and physicians (Villeneuve 2010). The primary outcome (change in LDL cholesterol level) was not reached after 12 months' follow up, nor was the secondary outcome (the proportion of patients achieving their target lipid levels). Key differences (in addition to the setting) between their intervention and our

SOS intervention included the direct contact between pharmacists and patients (5 consultations in the pharmacy over 12 months) rather than educational outreach by pharmacists to general practice staff. Community pharmacists modified statin dosages, after the GP had issued the initial prescription. The intervention did reduce LDL cholesterol (by 1.1mmol/l), but this did not reach statistical significance.

Chapter 7

Conclusion

The hypothesis that ‘primary care, general practice based pharmacists delivering the Statin Outreach Support intervention to general practices can increase the proportion of patients prescribed simvastatin 40mg with their cholesterol controlled’ has been confirmed.

The intervention worked for a combination of reasons, the most important of which were the time (duration) and effort (intensity) of the support provided by the pharmacists to practices. Individualisation of assistance at the GP, nurse and practice level, repetition of the main educational and practical messages, help given to practices to identify, call and recall suitable patients, the independence of the pharmacists from commercial or personal gain and good links with secondary care based experts all contributed to improving the uptake of the local cholesterol guideline. The key message for implementation included quality improvement and cost minimisation. This combination is intuitively acceptable to pharmacists delivering and practices receiving the support, and is likely to have contributed to the successful outcome.

Of note from the many subgroups found to benefit from the intervention, patients registered with practices in areas of greater socioeconomic deprivation and their Practice staff appeared to respond better. An explanation for this lies in the increased awareness among pharmacists, of the difficulties experienced by patients in areas of deprivation, and the hard work and time by pharmacists trying to systematically improve engagement and associated prescribing.

Chapter 8

Recommendations

Conditional on current prescribing and cholesterol management in primary care, the SOS intervention should be offered to practices allocated to the Usual Care arm.

The SOS model could be offered to other practices with baseline prescribing and cholesterol control comparable to baseline levels in the SOS trial.

Practices caring for patients in areas of socioeconomic deprivation are likely to benefit to a greater extent.

The Outreach Support model could be extended to focus on maximising the implementation of evidence in other therapeutic areas.

Follow up of clinical endpoints should be considered. In January 2012, participants from the SOS study will have reached 7 years follow up. With this length of follow up there is a possibility that the treatment effect between patients in the SOS intervention practices and UC has generated a statistically significant difference in morbidity/mortality outcomes. This length of follow up and improvement in important outcomes has not previously been shown in any educational outreach intervention study, or any previous pharmacist led intervention study. If these endpoints are improved, an economic analysis should be conducted, using data collected during the trial.

The findings should be submitted for publication in a mainstream medical journal.

Appendices

Appendix I

Mechanism of atherosclerosis and the effect of statins

'Plaques' are fatty deposits in blood vessels, which contribute to narrowing and vasoconstriction with resulting shortage of blood supply to the area beyond. If the area beyond is cardiac tissue then a heart attack is more likely or if the blood supply to the brain is affected then a stroke or transient ischaemic attack is likely. The deposits are made up of a range of constituents, including Low Density Lipoprotein (LDL) cholesterol and High Density Lipoprotein (HDL) cholesterol. These are two sub fractions found circulating in the blood supply. HDL is known to be protective while high relative levels of LDL increase the risk of vascular events.

Figures 1 and 2 describe some of the main processes thought to contribute to formation of atherosclerotic plaques, which are often found to be associated with vascular disease. The formation of LDL and HDL are key parts of the process, because their metabolic pathway has steps which can be targeted and inhibited in a way that stops their production, limiting the resulting plaques. One step in this process involves an enzyme called HMGCo enzyme A reductase.

(Adapted from A.D.A.M)

Figure 1. The effect of a raised LDL level

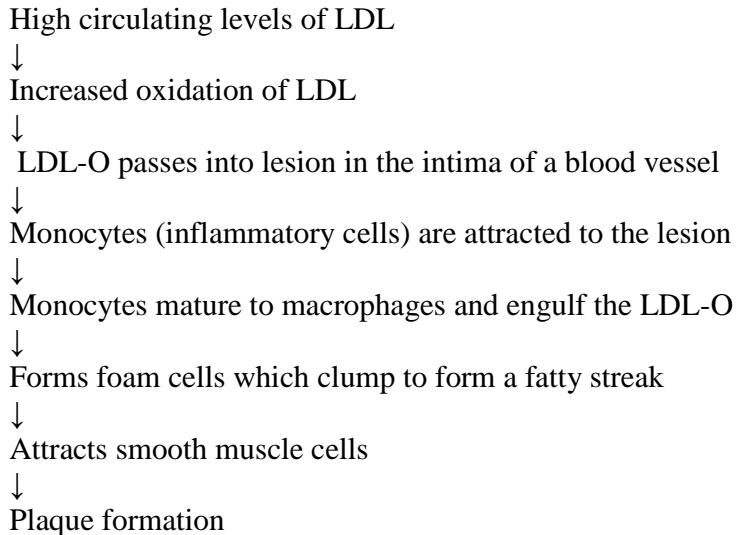
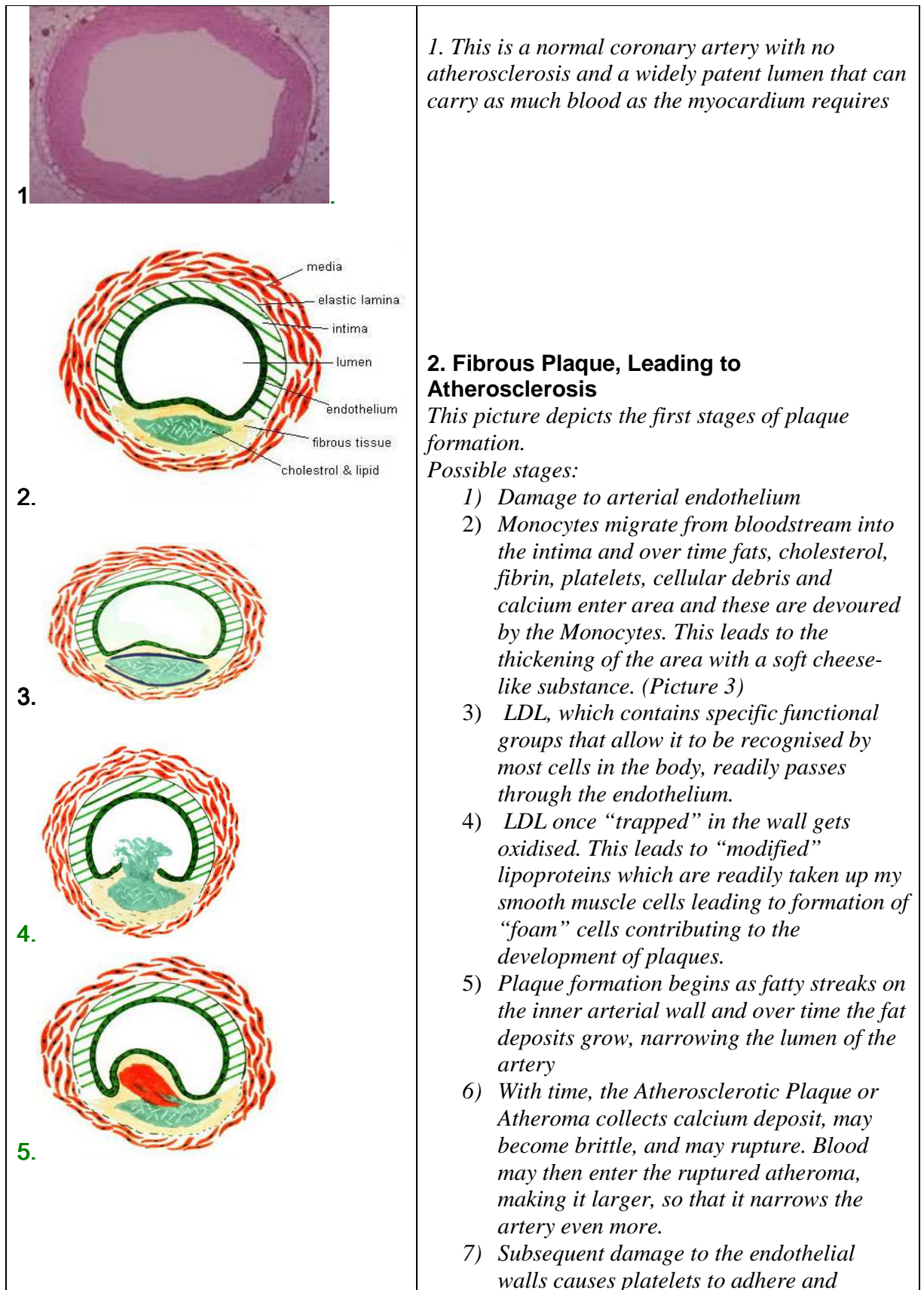



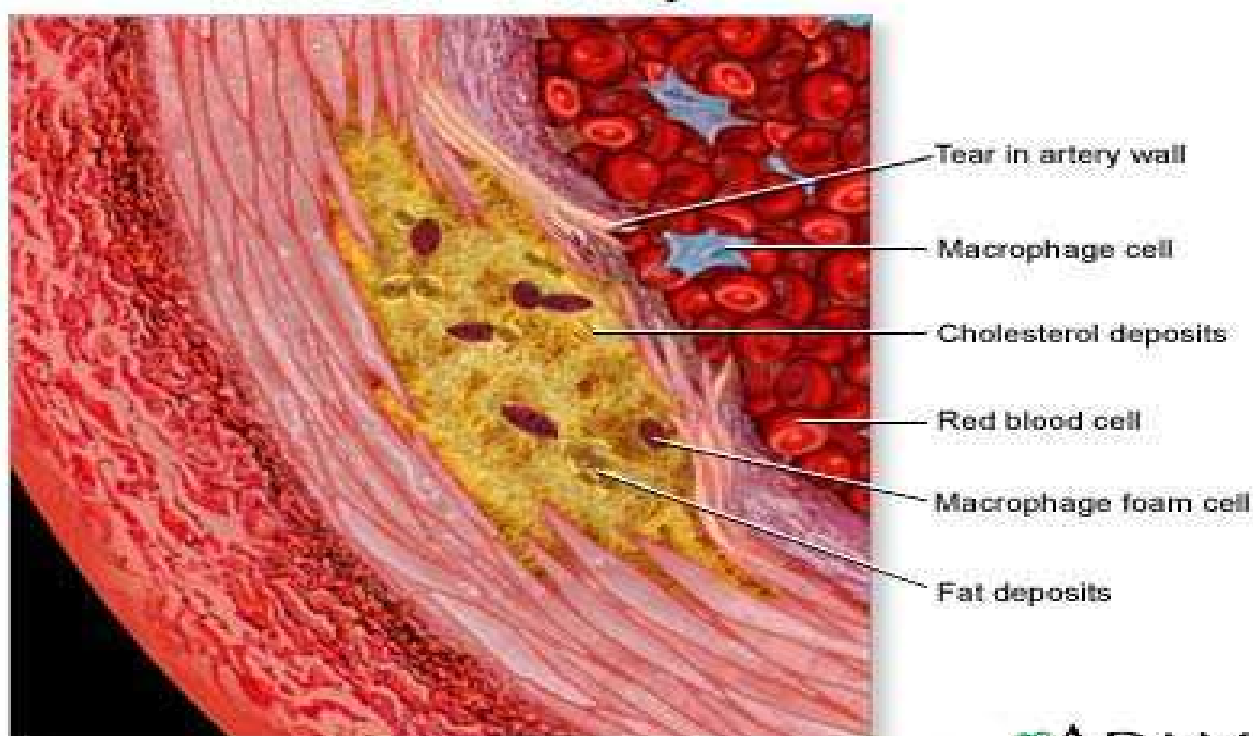
Figure 2. Formation of a fibrous plaque



<p>6-10.</p> 	<p>contributes to blood clot formation.</p> <p>8) A ruptured atheroma may also spill its fatty contents and trigger the formation of a blood clot (thrombus). The clot may further narrow or even occlude the artery, or it may detach and float downstream where it causes an occlusion (embolism).</p> <p>9) Surrounding muscle also proliferates to form larger plaques.</p> <p>10) Hardening of the arterial walls is due to various depositions within the plaque including lipids, cholesterol crystals and calcium salts. These depositions make the arteries bone like rigid tubes and very brittle.</p>
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An enlarged view of an atherosclerotic vessel

Cut-section of artery



ADAM.

How statins reduce cholesterol

On absorption from tablet form in the gastrointestinal tract, statins competitively inhibit HMGCo enzyme A reductase. The reductase enzyme is the rate limiting step in cholesterol synthesis in the liver, therefore statins reduce cholesterol synthesis in the liver (also in macrophages) thus decreasing the total cholesterol in the blood. Through a separate process, statins increase the number of LDL receptors in the liver which has the effect of binding more LDL and contributing to a lowering in this circulating (harmful) sub fraction. Dose dependent reductions in LDL cholesterol of 17-61% are common while there is a smaller reduction in plasma triglyceride and a small increase in HDL cholesterol.

In the process, when plaques do form on the intima of blood vessel walls, the plaques are less likely to rupture and cause harm, because the ratio of lipid is lowered. Over time, if statins are taken daily, existing plaques regress through a process of remodelling, but this is not thought to be the main reason for the beneficial effect, because benefits of statins precede the onset of remodelling.

Non lipid lowering effects of statins

These may also contribute to the beneficial effect, through modification of one or more of the following areas:

1. Blood vessel wall
2. Blood flow
3. Blood constituents

Blood vessel wall

Within the blood vessel wall, statins reduce cholesterol synthesis in macrophages and affect immune function, through an enzyme called Prostaglandin Generating Factor (PDGF) and an inflammatory marker called C - reactive protein (CRP). Macrophages synthesise cholesterol, carry oxidised LDL into the plaque, and stimulate smooth muscle cell growth, replication and plaque neovascularisation. They release cytokines and other inflammatory mediators which stimulate smooth muscle cells and plaque neovascularisation. Macrophages then release enzymes which weaken the cap of the plaque, causing increased risk of plaque rupture. In reducing cholesterol synthesis in macrophages, statins reduce macrophage activity. Statins also regulate and inhibit a number of natural cytotoxic agents in vitro and these observations are substantiated in clinical practice by the observation of reduced rejection at one year post cardiac transplant for patients receiving statins.

PDGF contributes to the migration of macrophages, platelets, smooth muscle cells and fibroblasts to atherosclerotic lesions. Statins inhibit PDGF induced DNA synthesis. High circulating CRP levels are an independent risk factor for atherosclerosis, primarily because CRP activates monocytes, which mature to macrophages.

Blood flow

One of the consequences of high cholesterol levels is an abnormality in the nitric oxide (NO) – L-arginine pathway with an inadequate supply of NO causing increased atherogenesis and thrombosis. Statins increase NO generation which causes vasodilation and improved blood flow. The use of statins improves endothelial function and vasomotion thus reducing myocardial ischaemia.

Blood constituents

Hypercholesterolaemia results in the following changes in the constituency of blood:

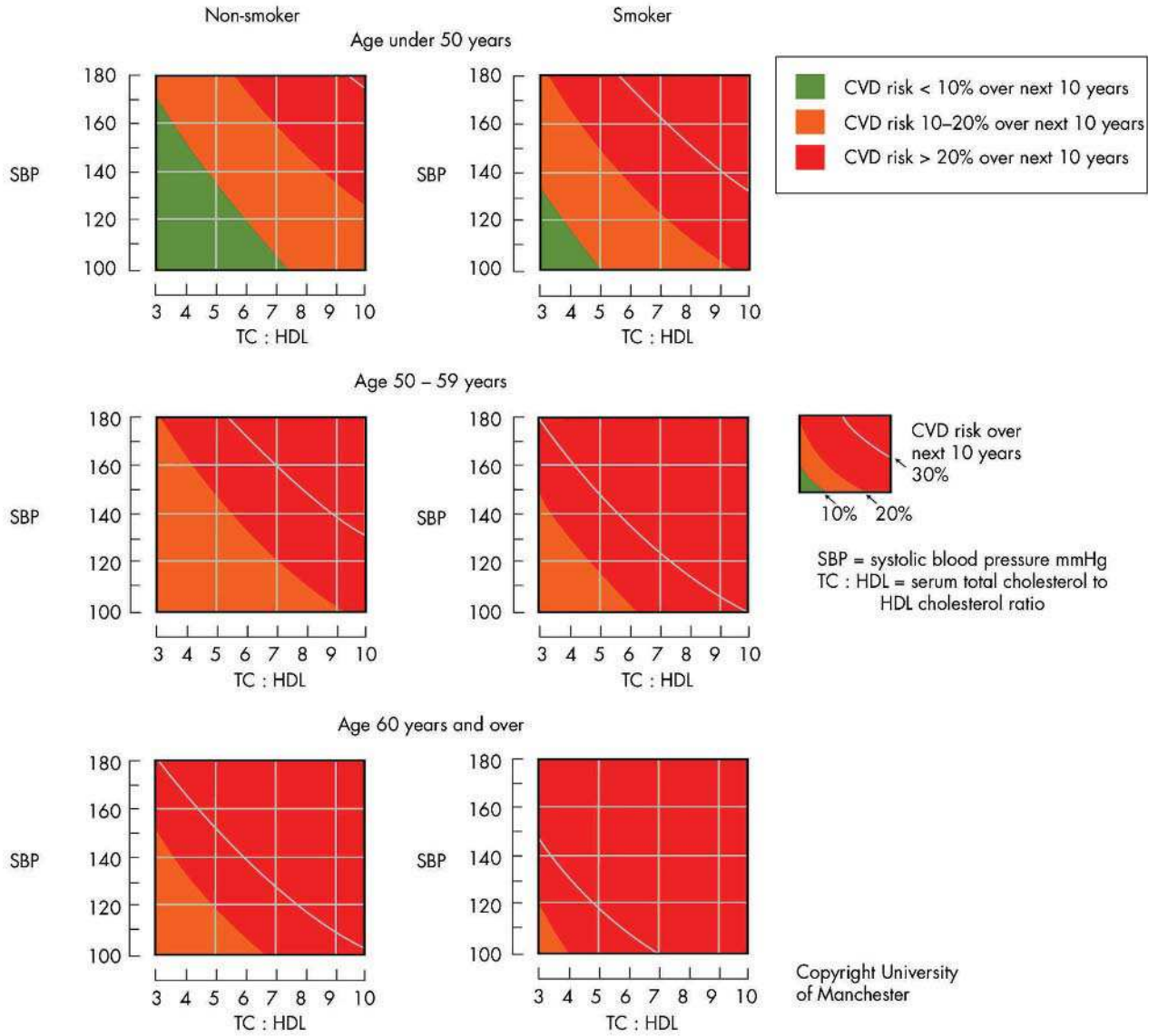
- Increased hypercoagulability
- Enhanced platelet reactivity at the site of acute vascular damage due to the alteration of the calcium content of the platelet cell membrane
- Increased fibrinogen (a key factor in the blood clotting cascade pathway) levels

The consequence of hypercholesterolaemia is therefore increased thrombus formation on plaque rupture. Statin effects upon blood constituents include decreased fibrinogen levels and reduced ADP-induced aggregation of platelets.

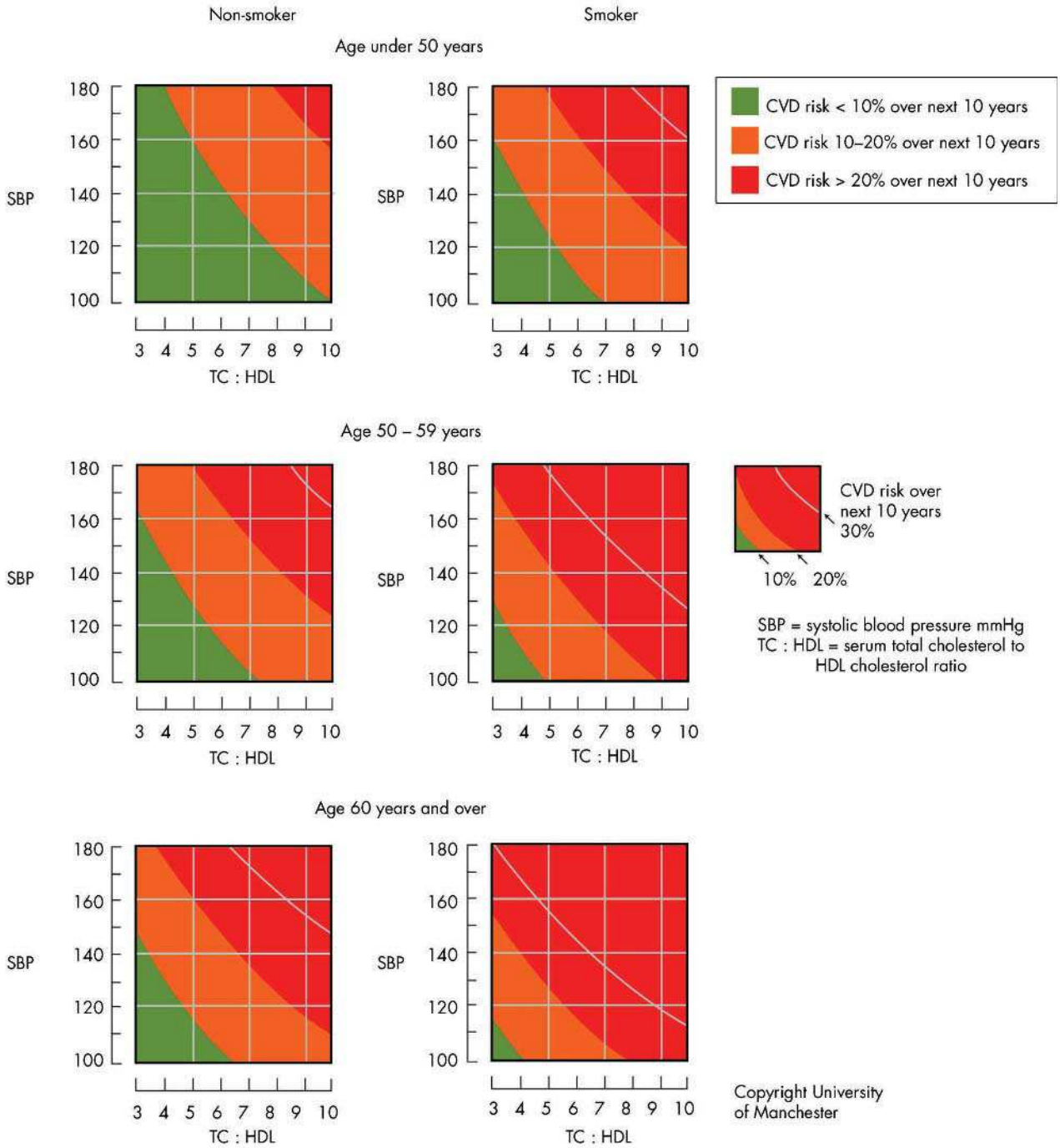
Appendix II

Cardiovascular disease risk predictor

NON-DIABETIC MEN



NON-DIABETIC WOMEN



Appendix III

Heart Protection Study – Subgroups for 1st vascular event (CHD / CVA / revascularisation)

Category	N	Placebo	Simvastatin	ARR	NNT
Coronary Heart Disease	13386	27.5%	21.8%	5.7%	18
Any PVD	6748	32.7%	26.4%	6.3%	16
PVD alone	2701	30.5%	24.7%	5.8%	17
CVA (any stroke)	3280	29.8%	24.7%	5.1%	20
CVA (stroke alone)	1820	23.6%	18.7%	4.9%	20
Diabetes Mellitus (any diabetes)	5963	25.1%	20.2%	4.9%	20
Diabetes Mellitus (diabetes alone)	3982	18.6%	13.8%	4.8%	21
Total Cholesterol <5	4072	23.1%	17.7%	5.4%	19
Total Cholesterol ≥5 but <6	7883	24.5%	18.9%	5.6%	18
Total Cholesterol ≥6	8581	26.8%	21.6%	5.2%	19

ARR=absolute risk reduction; NNT=number needed to treat for 5 years to prevent one event

Appendix IV

Cholesterol guidelines (pre-HPS era)

UK guidelines

The joint recommendations of the British Cardiac and Hypertension Societies and the British Hyperlipidaemia and Diabetic Associations, published in 1998, advised estimating the absolute risk of CHD using Framingham based criteria, which include HDL cholesterol as a variable. Coronary risk charts are readily available, which allow identification of individuals at risk of a coronary event. Priority for treatment was given to those with established CHD or with an estimated risk of $\geq 15\%$ over the following 10 years. All individuals in these categories with serum total cholesterol $\geq 5\text{mmol/l}$ or LDL cholesterol $\geq 3\text{mmol/l}$ should receive lifestyle advice aiming to reduce the values to $< 5\text{mmol/l}$ and $< 3\text{mmol/l}$ respectively. Lipid lowering treatment was recommended for those whose cholesterol remained above the threshold. Since then, more recent guidance appeared for England and Wales in the National Service Framework for CHD (Department of Health 2000), and in Scotland, in the Scottish Intercollegiate Guideline Network. These recommended that patients with CHD or at high risk (defined as $\geq 30\%$ over 10 years) should be managed by diet and statins with the aim of lowering serum total cholesterol below 5mmol/l or by 20-25%, whichever would result in the lowest level.

European guidelines

The Third Joint Task Force of European and Other Societies' guidelines focus on the prevention of fatal CVD rather than CHD events (De Backer 2003). Assessment of CVD risk is based on the systematic coronary risk evaluation score system, high risk being defined as $\geq 5\%$ chance of fatal CVD within 10 years. High risk subjects should have their total and LDL cholesterol lowered to less than 5mmol/l and 3mmol/l respectively, unless they have overt CVD, diabetes or serum total and LDL cholesterol concentrations which are already below these values, in which case the targets are lowered to $< 4.5\text{mmol/l}$ and $< 2.5\text{mmol/l}$ respectively.

North American guidelines

The third report of the National Cholesterol Education programme (NCEP) reiterated the use of the LDL cholesterol reading as the criterion for when to initiate treatment and as a therapeutic goal. The greater the risk of CHD, the lower the concentration of LDL cholesterol at which treatment is initiated, and the lower the target level (Expert panel on detection, evaluation and treatment of high cholesterol in adults 2001). Patients with CHD, diabetes or multiple risk factors conferring a 10 year risk of CHD of $> 20\%$ over 10 years are deemed to be at high risk. Most people will require lipid lowering drug therapy to achieve the LDL cholesterol goal of $< 2.6\text{mmol/l}$ but therapeutic lifestyle changes may achieve the less severe targets of $< 4.1\text{mmol/l}$ and $< 3.4\text{mmol/l}$ recommended for those at low and moderate risk respectively.

Appendix V

MEDLINE search terms

<ol style="list-style-type: none"> 1. Prescriptions, Drug/ or prescribing.mp. 2. Education, Medical, Continuing/ or academic detailing.mp. 3. facilitation.mp. or SOCIAL FACILITATION/ 4. outreach visit\$.mp. 5. 1 and (2 or 3 or 4) 6. limit 5 to humans 7. Meta-Analysis/ 8. meta analy\$.tw. 9. metaanaly\$.tw. 10. meta analysis.pt. 11. (systematic adj (review\$1 or overview\$1)).tw. 12. exp Review Literature/ 13. or/7-12 14. □harmacy.ab. 15. embase.ab. 16. (psyclit or psychlit).ab. 17. (psycinfo or psychinfo).ab. 18. (cinahl or cinhal).ab. 19. science citation index.ab. 20. bids.ab. 21. cancerlit.ab. 22. or/14-21 23. reference list\$.ab. 24. □harmacy□e□y\$.ab. 25. hand-search\$.ab. 26. relevant journals.ab. 27. manual search\$.ab. 28. or/23-27 29. selection criteria.ab. 30. data extraction.ab. 31. 29 or 30 32. review.pt. 33. 31 and 32 34. comment.pt. 35. letter.pt. 36. editorial.pt. 37. animal/ 38. human/ 39. 37 not (37 and 38) 40. or/34-36,39 41. 13 or 22 or 28 or 33 42. 41 not 40 43. Randomised Controlled Trials/ 44. randomised controlled trial.pt. 45. Random Allocation/ 46. Double Blind Method/ 47. Single Blind Method/ 48. clinical trial.pt. 49. exp Clinical Trials/ 50. or/43-49 51. (clinic adj trial\$1).tw. 52. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw. 53. PLACEBOS/ 54. placebo\$.tw. 55. randomly allocated.tw. 56. (allocated adj2 random).tw. 57. or/51-56 58. 50 or 57 59. case report.tw. 60. letter.pt. 61. historical article.pt. 62. review of reported cases.pt. 63. review, multicase.pt. 	<ol style="list-style-type: none"> 64. or/59-63 65. 58 not 64 66. ECONOMICS/ 67. "Costs and Cost Analysis"/ 68. Cost Allocation/ 69. Cost-Benefit Analysis/ 70. Cost Control/ 71. Cost Savings/ 72. Cost of Illness/ 73. Cost Sharing/ 74. "Deductibles and Coinsurance"/ 75. Medical Savings Accounts/ 76. Health Care Costs/ 77. Direct Service Costs/ 78. Drug Costs/ 79. Employer Health Costs/ 80. Hospital Costs/ 81. Health Expenditures/ 82. Capital Expenditures/ 83. Value of Life/ 84. exp Economics, Hospital/ 85. exp Economics, Medical/ 86. Economics, Nursing/ 87. Economics, Pharmaceutical/ 88. exp "Fees and Charges"/ 89. exp BUDGETS/ 90. (low adj cost).mp. 91. (high adj cost).mp. 92. (health?care adj cost\$.mp). 93. (fiscal or funding or financial or finance).tw. 94. (cost adj estimate\$.mp). 95. (cost adj variable).mp. 96. (unit adj cost\$.mp). 97. (economic\$ or pharmacoeconomic\$ or price\$ or pricing).tw. 98. or/66-97 99. 65 or 64 or 98 100. 6 and 99 101. □harmacy□e\$.mp. 102. exp Education, Professional/ 103. exp Drug Utilization/ 104. exp Professional Practice/ 105. 1 or 103 106. 2 or 3 or 4 or 101 or 102 or 104 107. 105 and 106 108. 107 and 99 109. limit 108 to humans 110. exp family practice/ 111. exp physicians, family/ 112. exp primary health care/ 113. exp community medicine/ 114. (general adj pract\$.ti,ab. 115. exp community health services/ 116. exp community pharmacy services/ 117. exp primary nursing care/ 118. (community adj3 (□harmacy\$ or nurse\$ or nursing or care or practice)).ti. 119. (primary adj3 (care or nurse\$ or nursing or practice)).ti. 120. ((general or gp) adj1 (practice or practitioner\$1)).ti. 121. ((practice or district or practitioner\$1) adj1 (nurse\$1 or nursing)).ti. 122. (health adj visitor\$1).ti. 123. gps.ti. 124. or/110-123 125. 109 and 124
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Appendix VI

Ethical approval

GREATER GLASGOW COMMUNITY/PRIMARY CARE
LOCAL RESEARCH ETHICS COMMITTEE

Chairman: Rev. L. Fisher
Deputy: Dr. M. Sharif
Administrator: Mrs. H. Illingworth
(Direct Line: 0141 211 1658)

17 December 2002

Richard Lowrie
Clinical Pharmacy Dept
PCT Trust Headquarters
Gartnavel Royal Hospital
Great Western Road
Glasgow

Dear Richard

A study of the effectiveness and cost effectiveness of clinical pharmacist facilitation to address inappropriate prescribing of statins in general practice

At its meeting on 12th December 2002, the Committee gave approval for the above study to proceed in this area with the participation of yourself.

Yours sincerely



Rev L Fisher
Chairman

Appendix VII

Cholesterol control at baseline

Practice ID	Number per practice	Number of eligible patients with cholesterol not controlled (%)	Number of eligible patients with cholesterol controlled (%)
1	253	213 (84.2)	40 (15.8)
2	155	108 (69.7)	47 (30.3)
3	296	202 (68.2)	94 (31.8)
4	100	69 (69.0)	31 (31.0)
5	255	176 (69.0)	79 (31.0)
6	117	76 (65.0)	41 (35.0)
7	234	141 (60.3)	93 (39.7)
8	133	74 (55.6)	59 (44.4)
9	216	144 (66.7)	72 (33.3)
10	261	171 (65.5)	90 (34.5)
11	215	125(58.1)	90 (41.9)
12	132	77 (58.3)	55 (41.7)
13	80	48 (60.0)	32 (40.0)
14	237	125 (52.7)	112 (47.3)
15	90	48 (53.3)	42 (46.7)
16	108	38 (35.2)	70 (64.8)
17 [§]	57	43 (75.4)	14 (24.6)
18	63	49 (77.8)	14 (22.2)
19	135	94 (69.6)	41 (30.4)
20	33	21 (63.6)	12 (36.4)
21	53	34 (64.2)	19 (35.8)
22	57	38 (66.7)	19(33.3)
23	76	48 (63.2)	28 (36.8)
24	89	52 (58.4)	37 (41.6)
25	97	47 (48.4)	50 (51.6)
26	39	18 (46.2)	21 (53.8)
27	50	21 (42.0)	29 (58.0)
28	114	54 (47.4)	60 (52.6)
29	63	28 (44.4)	35 (55.6)
30	133	63 (47.4)	70 (52.6)
31	99	34 (34.3)	65 (65.7)
	4040	2479 (61.4)	1561 (38.6)

[§] Practice disbanded prior to randomization, unknown to the research team until after randomization

Appendix VIII

Secondary prevention of coronary heart disease and stroke

Patients with established atherosclerotic disease are at high risk and should be treated with a statin regardless of total blood cholesterol concentration

i.e. Previous MI / pre- or post-CABG / pre- or post-Angioplasty / Angina / Angiographic coronary artery disease / Ischaemic stroke or TIA / Peripheral Arterial Disease / Patients with diabetes aged ≥ 40 years

Random non-fasting test for total cholesterol and LFT's*

**Do within 24 hours of onset of acute MI*

Consider secondary causes & familial hyperlipidaemia if Cholesterol >8.0 mmol/L[†]

† Discuss with lipid clinic if in doubt

Treat all patients with statin regardless of baseline cholesterol concentration

Recommended drug & daily dose

Simvastatin 40mg daily

Consider Atorvastatin 80mg in acute coronary syndrome with elevated troponin

See BNF for cautions, contra-indications and clinically important interactions.

Re-test at 1 month

Random non-fasting total cholesterol + triglycerides + LFT's

GOALS OF TREATMENT BY THREE MONTHS

Total cholesterol concentration <5.00 mmol/l
(<4.2 mmol/L for post CABG patients)

AND

Reduce cholesterol concentration by $\geq 25\%$

Triglycerides > 4.0 mmol/L

Check fasting sample[‡]

Cholesterol Goals Achieved

Annual review to ensure continued concordance.

Cholesterol goals not achieved

Discuss concordance. Switch to Atorvastatin 40 – 80mg depending on response. Consider addition of ezetimibe if necessary. The use of other lipid-lowering agents is not recommended without specialist advice.

[‡] Consider referral to lipid clinic in resistant cases, if liver transaminases $> 2x$ normal, or if statin not tolerated.

ATHEROSCLEROTIC ARTERIAL DISEASE IS OF MULTIFACTORIAL ORIGIN. NO SINGLE RISK FACTOR, INCLUDING CHOLESTEROL CONCENTRATION, SHOULD BE VIEWED IN ISOLATION.

- Encourage smoking cessation (consider nicotine replacement therapy)
- All other risk factors hypertension, diabetic control, should be addressed (see separate guidelines)
- Aspirin 75mg (not enteric coated) should be taken by all those with occlusive arterial disease in the absence of contraindications (active peptic ulceration, a bleeding disorder or true hypersensitivity)
- Consider treatment with ACE-inhibitors especially in patients with left ventricular dysfunction or heart failure

Appendix IX

Baseline Data Collection

Practice ID:

Today's date:.....

Patient I.D.:

DOB:

M / F

1. Relevant Diagnoses

Secondary prevention	definite	possible	Primary Prevention	yes	no	unclear
Previous MI/ Date:	<input type="checkbox"/>	<input type="checkbox"/>	Hypertension: Syst >160 or Diast >90 or on antihypertensive therapy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pre/Post CABG/ Date:	<input type="checkbox"/>	<input type="checkbox"/>				
Pre/Post Angioplasty/ Date:	<input type="checkbox"/>	<input type="checkbox"/>	FH of CHD: Father <45yrs or Mother <55yrs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Angina / IHD/ Date:	<input type="checkbox"/>	<input type="checkbox"/>				
PVD/ Intermittent claudication/ Date:	<input type="checkbox"/>	<input type="checkbox"/>	Smoker	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Diabetes/ Date:	<input type="checkbox"/>	<input type="checkbox"/>	Other (specify):			
Stroke/Date:	<input type="checkbox"/>	<input type="checkbox"/>				
TIA/ Date:	<input type="checkbox"/>	<input type="checkbox"/>				

2. About the statin prescription...

Statin:

- None
- Simvastatin
- Pravastatin
- Atorvastatin
- Fluvastatin
- Other:

Dose

- 10mg
- 20mg
- 40mg
- 80mg
- Other:

Current Cholesterol level :

.....mmol/l (LDL
.....HDL.....)

Date.....
or
None

Appendix X

Allocation schedule

Practices [‡]	Allocation	
	SOS	Usual Care
G1	(1,1)	
G2		(1,0)
G3	(2,1)	
G4		(2,0)
G5	(3,1)	
G6		(3,0)
G7	(4,1)	
G8		(4,0)
G9		(5,0)
G10	(5,1)	
G11	(6,1)	
G12		(6,0)
G13		(7,0)
G14	(7,1)	
G15	(8,1)	
G16		(8,0)
S1	(1,1)	
S2		(1,0)
S3		(2,0)
S4	(2,1)	
S5	(3,1)	
S6		(3,0)
S7		(4,0)
S8	(4,1)	
S9	(5,1)	
S10		(5,0)
S11		(6,0)
S12	(6,1)	
S13	(7,1)	
S14		(7,0)

Practices are shown in the pairs resulting from stratification.

[‡]G = Group, SH = single handed. The disbanded SH practice had been part of the only triple, allocated to the SOS arm.

Appendix XI

Clinical Facilitation: a summary for practices

This is a multifaceted intervention, rooted in the belief that more intensive efforts to alter prescribing practice are generally more successful. Clinical Facilitation[§] involves prescribing support pharmacists meeting individually with GPs or nurses to identify any obstacles standing in the way of offering patients statins to lower cholesterol and then providing specific, practical solutions (facilitation) to overcome these obstacles. Some techniques used to reach agreement on what support is required to address gaps in the implementation of the evidence may include a practice based clinical audit, open, honest communication and an acknowledgement of what may be required to change prescribing practice and patient attendance. Increasing the extent of implementation of local guidelines encouraging the prescribing of simvastatin 40mg for patients with vascular disease will feature in each meeting.

Pre – meeting 1

Prior to meeting 1, the pharmacist searches the practice computer to ascertain numbers of patients with confirmed vascular disease who are not treated with statins in line with the local guideline.

Meeting 1 (up to 30 minutes)

Outline of process. Identification of GP/nurse learning needs (knowledge based or organisational) and identification of each practitioner's preferred learning method. The information gathered pre meeting 1 is summarised, displayed graphically and shared with the GP/nurse during the first meeting. If expert opinion is requested to address uncertainties in therapeutic management, this is sought and incorporated into the second meeting. Discussion of need and methods to address the gap between guideline and implementation.

Key outcome: Agreement on individual information /practice organisational barriers that prevent the identified patients with vascular disease being identified and offered statins. Targets for changes in prescribing are discussed and agreed if possible.

Meeting 2 (up to 1 hour)

Interactive, individualised presentation by pharmacist facilitator. Delivery of therapeutic information about the practice's prescribing of statins and summarised trial information in a concise, unbiased, understandable format. The pharmacist suggests and seeks agreement for solutions to questions/barriers raised at 1st meeting. Anonymised patient specific prescribing and clinical data are used to simulate therapeutic challenges. The pharmacist will offer the views of respected peers/specialists.

Key outcome: Commitment by the GP/nurse to changing their approach to prescribing statins for patients identified pre meeting 1, with vascular disease, with or without a statin. Responsibilities for behavioural change and timelines for action agreed. If agreed action involves the pharmacist committing to ongoing support for creating a register of patients with vascular disease, the pharmacist agrees when this can be done. Pharmacist will then facilitate change by visiting the practice weekly until the agreed actions are carried out. The actions may involve the identification of suitable patients followed by mailing of letters to patients explaining benefits of statins and requesting the patient's attendance at clinic for a review.

Meeting 3 (up to 30 minutes)

Positive reinforcement of changes made since meeting 2. The pharmacist searches the practice computer system to identify a sample of patients with coronary heart disease to assess the impact of the facilitation process. Key messages are repeated. Additional barriers to change management are identified and addressed. Graphical presentation of how the practice's prescribing statistics have changed is fed back.

Key outcome: Practice agree ongoing, systematic approach to optimising statin use in line with guideline

§ Statin Outreach Support, SOS

Appendix XII

Example of power point presentation for SOS meeting

Statin Outreach Support Project

Dr XXX & Partners

March 2004: Meeting 2

Information For Dr XXX

MEETING 1-Summary

- Gathered information about your statin use
- Briefly discussed the HPS & proposed new Glasgow guidelines on cholesterol management
- Agreed in principal to increased prescribing of simvastatin 40mg
- Identified the information you would like to receive to bring you up to speed with the current evidence
- You requested specific information about:
 - cholesterol management in the elderly
 - In those with excess alcohol intake.
 - if there was a level of cholesterol below which it becomes harmful

What's happened since Meeting 1?

- Formal launch of the new Guidelines on Cholesterol Management
- We have looked for answers to some of your queries from a variety of expert sources:
 - Consultants Miles Fisher & Stuart Cobb
 - GRI Drug Information
 - Biochemist at Western Infirmary
 - Extensive Literature Search

Objectives to be met in meeting 2

- Delivery of a concise summary of the Key Outcomes of the Heart Protection Study
- Highlight the important changes to the Glasgow guidelines on cholesterol management and underline how this will affect your current working practice
- Answer specific questions
- Put forward a workable plan to implement the new guidelines in current and future patients with established vascular disease

My Proposal/Overall Aim

- To ensure all your current and future patients with vascular disease are offered 40mg Simvastatin

Why is this important ?

- There's a big problem out there!
- Here in Shettleston:

38% greater incidence of Heart Disease than Scottish average*

40% greater incidence of Stroke than Scottish average**

*Worst incidence of all Glasgow Wards

**Second worst for stroke

Good reasons for tackling the problem now

- Our patients will quickly benefit:
 - Strong evidence from the HPS - 25% reduction in risk of major vascular event
 - This means If we prescribe Simvastatin 40 for all currently **untreated** vascular patients in this Practice (n=178) we will prevent (at the very minimum)
 - **9 major vascular events**
 - **3 deaths**

- Practice will benefit financially:
- Baseline audit:
 - 17% of your vascular disease patients currently have a chol <5mmol/l
- GP contract requires:
 - 90% with cholesterol level noted in previous 15 months
 - 60% with a cholesterol <5mmol/l

GP Contract points

Information requested

- HPS key outcomes
 - Learning Points
 - **Who is classified as having established vascular disease**
 - **Who should be treated with a statin**

- Update on Glasgow Primary and Secondary prevention guidelines
 - Learning Point
 - **Understand the difference in absolute risk between primary and secondary prevention candidates**
 - **Importance of using Joint Risk Charts**

How do Statins work?

- HMGCoA reductase Inhibitors
- Act by blocking the key enzyme in the production of cholesterol in the liver
- The resultant fall in circulating cholesterol levels stimulates an increase in the expression of LDL-receptors that remove circulating LDL from the blood
- End result is a fall in LDL cholesterol (range 25-60%) and hence total cholesterol

Mode of Action of Statins in lowering cholesterol

Do statins have any other important actions?

Non-cholesterol lowering effects of statins

- **Inhibit macrophages**
 - stabilise atherosclerotic plaque
- **Inhibit natural cytotoxic agents**
 - ↓ transplant rejection
- **Inhibit PDGF/Fibrinogen**
 - reduced thrombus formation
- **Increased NO formation**
 - ↑ vasodilation/blood flow
- **Reduced CRP**
 - independent risk factor for atherosclerosis

Which Statin, Which dose?

- There are more potent statins than Simvastatin
 - Atorvastatin
 - **There is limited safety data on Atorvastatin**
 - **Limited mortality data**
 - **Less cost effective**
 - Rosuvastatin
 - **No information on mortality or morbidity**
 - **?Concerns over safety**

GGHB Drug of Choice

- Simvastatin 40mg
 - Safe
 - Effective –lowers LDL by ~40%
 - Morbidity & Mortality data available
 - Now off Patent
 - Most Cost Effective choice

Let's look at the evidence for Simvastatin 40mg

- Heart Protection Study (HPS)
- Data sheet
- Other studies

HPS

- Largest trial of cholesterol-lowering in the world – Used Simvastatin 40mg in Over 20,000 patients for 5 years
- Included a wide range of patient groups:
 - **CHD (MI, angina, CABG, PTCA)**
 - **TIA, CVA**
 - **PVD**
 - **Diabetic patients over 40 (with and without CHD)**
- Wide age range 40-80 years
- 25% were women
- *Inclusion criteria: total cholesterol ≥ 3.5 mmol/l

Key Outcomes from HPS

- Simvastatin 40mg reduced the risk of a major vascular event by 25%
- Risk reduction seen in **ALL** categories of patients:
 - **old/young;**
 - **male/female;**
 - **PVD**
 - **CHD**
 - **TIA/CVA**
 - **Diabetes (with and without CHD)**
 - **Those with “normal cholesterol”**

Important Point 1:

Patients NOW recognised as having established Vascular Disease:

- Post MI Angina Angioplasty Diabetics (>45 yrs old) Stroke/TIA PVD CABG

Important Point 2:

- ****Treat patients on basis of risk NOT cholesterol level****
- **Start simvastatin 40mg in all vascular patients whether cholesterol is raised or not**

Main Message from HPS

- Adding Simvastatin 40mg to existing treatment* SAFELY produces substantial **additional** benefits for a wide range of high risk patients, **irrespective** of their initial cholesterol level.
- **NNT=19**

Safety of Simvastatin 40mg

- Serious adverse effects (development of abnormal Liver function or muscle damage) was very rare during the HPS study.
- No significant difference in incidence between **active** and **placebo** arms – in the number of participants who stopped treatment because of elevated LFTs or muscle symptoms (0.5% vs 0.3% and 0.5 vs 0.5% respectively)

Myopathy/Rhabdomyolysis (data sheet)

- Risk of Myopathy is dose related and rare
 - Incidence:
 - **0.02% at 20mg**
 - **0.07% at 40mg**
 - **0.3% at 80mg**

*If myopathy occurs (CK>10 times ULN) STOP STATIN

*If muscle pain and CK >3 times ULN, stop, re-measure and once normalised can try dose reduction or different statin. Monitor more closely

- Risk of myopathy increased with concurrent Amiodarone or Verapamil
 - Recommend maximum dose of 20mg simvastatin
- Risk of myopathy increased with concurrent erythromycin, clarithromycin, itraconazole, ketoconazole
 - Suspend simvastatin until course is finished

Statins in those with deranged liver function

- HPS excluded patients with chronic liver disease (cirrhosis or hepatitis) or ALT >1.5x ULN
- Glasgow Guideline: consider referral to lipid clinic if ALT >2 x ULN
- Data sheet: C/I in **ACTIVE** liver disease or unexplained persistent elevation of serum transaminases (ALT, AST).
- Data sheet: Caution in patients predisposed to rhabdomyolysis – this includes those who **abuse alcohol** –check CK prior to starting

Statins in the Elderly (>65yrs)

- Absolute coronary risk increases with age
- Over 25,000 patients >65 years old have been included in well done clinical trials (pooled data)
- Risk reduction in the elderly taking statins is at least as good than in middle-aged adults
- HPS has provided evidence of benefit up to 85 years of age (28% over 70yrs at entry).
- On completion of HPS & Prosper the oldest patients were 85 yrs
- **BUT** The frail, elderly should be considered on an individual basis

Side effects in the elderly

Opinion of Dr John Byrne (Cardiologist S/General):

- “The elderly are more prone to side effects with most drugs BUT for statins, it is important to remember the benefits are substantial for secondary prevention”
- No documented evidence incidence of side effects from statins is higher in the elderly

Other side effects

- Very well tolerated overall. Incidence of side effects seems to be around 1%
- Minor Side effects are relatively uncommon and may be dose related. If they occur and cannot be tolerated try reducing the dose or try another statin
- Rash- withdraw treatment, if resolves try another statin. If rash not related to statin, restart simvastatin 40mg

Monitoring-What and how often?

- HPS demonstrated excellent safety of simvastatin 40mg
- HPS advocates starting simvastatin in high risk patients regardless of initial cholesterol level
- The majority of patients will reach target cholesterol level on this dose
- Do we need regular monitoring of cholesterol or LFTs?

Monitoring- Why do we need it?

- Glasgow Guidelines advocate baseline recording of Cholesterol and LFTs then repeat after 1-3 months
- GP Contract wants baseline Cholest and LFTs (within previous 15 months)
- Evidence that regular monitoring improves compliance
- Checks desired outcome achieved

Primary vs. Secondary prevention

- Need to think about absolute risk when prescribing statins:
 - NNT for 5 years to avoid a vascular event in a patient with IHD = 26 (secondary prevention)
 - **These patients are at HIGH risk $\geq 30\%$ in 10 years**
 - NNT for 5 years to avoid a vascular event in a patient with hypertension and no other risk factors = 125 (primary prevention)
 - **This patient is at much lower risk $\leq 5\%$ in 10 years**

Prescribing Simvastatin 40mg for Primary Prevention

- Primary prevention is for patients with NO EVIDENCE of established vascular disease but the presence of risk factors
 - Hypertension
 - Hypercholesterolaemia
 - smoking
 - Diabetes (if <40)
- Use joint risk charts to work out 10 year risk. START SIMVASTATIN 40MG ONLY IF RISK IS $>30\%$ OVER 10 YEARS

New Glasgow guidelines for cholesterol management

- The Glasgow Guidelines have changed in response to the KEY OUTCOMES from the HPS
- Both the Primary Prevention AND Secondary Prevention guidelines have changed

Update on Glasgow Cholesterol management guidelines

- **Old secondary prevention guidelines:**
 - Considered established CHD patients only (MI, angina, CABG, angioplasty)
 - Commence statin only if cholesterol $>5^*$
 - Start statin at lowest dose and titrate up
 - Aim for cholesterol level $<5^*$ and at least 1mmol/l reduction

Update on Glasgow Cholesterol management guidelines

- **Updated secondary prevention guidelines (January 2004):**
 - Consider **ALL** patients with vascular disease (CHD, CVA/TIA, PVD, diabetics over 45years) to be at HIGH RISK
 - No need to titrate- Commence Simvastatin 40mg REGARDLESS of cholesterol level
 - Aim for chol level $<5^*$ and at least 1mmol/l reduction

Implementing the evidence-base in this Practice

Patients with vascular disease NOT on a statin (178)

Process:

- Jan to produce updated list for screening
- GP to review list to exclude unsuitable patients
- Jan to draft invite letter proposing statin initiation and inviting patient to surgery for bloods before starting
- Approval of letter
- send 20 letters/week (copy in notes and flag notes for opportunistic initiation)
- Practice nurse/GP to see for baseline bloods and sales pitch
- GP to confirm LFTs ok and Rx Simvastatin 40mg
- identify non attenders and follow up (phone etc)

Implementing the evidence-base in this Practice

- Patients with vascular disease on lower dose statin but not at target (117)
 - Jan to produce updated list for screening
 - Jan to draft letter proposing dose increase and/or invite for bloods if no level in last 15 month
 - 1. send all letters where only script required and put approx retest appointment time (staggered)
 - 2. send 20 letters/wk with letter +invite for bloods and tag notes for opportunistic dose increase
 - Practice nurse/GP to see for updated baseline bloods and sales pitch
 - GP –confirm LFTs ok, change to Simvastatin 40mg [*or other]
 - Jan to identify non attenders and follow up

Current Statin Use

Aims for the future?

Proposal

- To ensure all your current and future patients with vascular disease are offered 40mg Simvastatin

SUMMARY -Why Simvastatin 40mg

- HPS (and 4S) confirms tolerability and SAFETY and positive morbidity/mortality benefits (not just cholesterol lowering) in >25,000 patients
- Simvastatin is now off patent and in Drug-tariff: price has already fallen substantially in current drug tariff and will fall further
- **Simvastatin** is the GGB drug of choice for lowering cholesterol in both Primary and secondary prevention
- **Simvastatin 40mg is most cost-effective option for both primary and secondary prevention**

Appendix XIII

Pharmacists' training regimen

Training day	Aim	Objective	Learning methods	Assessment method
1 st September 2003	To become a credible expert in statin use and evidence base	To develop understanding of the HPS and Glasgow Guidelines, and likely reasons for lack of uptake at practice and patient level To complete a critical appraisal on the HPS, and to be able to describe the rationale, methods and results	-Self directed study. - Protected time to read and learn relevant published research and understand rationale and application of Glasgow statin guidelines - Didactic lecture from cardiologist -Critical appraisal checklist for HPS - One to one discussion with principle investigator, covering completed checklist, with feedback - identification of additional learning needs	- One to one discussion with principal investigator. - Completion of questions on HPS, answers assessed by principal investigator. - Evidence that the pharmacist has considered potential barriers to uptake and ways to overcome these
30 th September 2003				- Detailed, accurate understanding of HPS
9 th and 16 th October 2003	To develop fluency in describing the costs and benefits of rational statin treatment for vascular disease	To learn and be able to describe the rationale, need, therapeutic indications, side effects, costs and benefits of statins for vascular disease	- Interactive lecture by a GP/ Educationalist/Professor of General Practice/Primary Care on Adult learning and Problem Based learning - Group discussion - In pairs, completion of a problem based learning task	Evaluation of performance by two experienced GPs and a Practice Nurse with special interest in cardiology
28 th October 2003	Educational Outreach and SOS trial methodology	To develop understanding of the methods adopted for educational outreach.	- role play - Didactic lectures	Evaluation of performance by GP/lecturer in Department of General Practice and Primary Care
1 st November 2003	SOS delivery	To become familiar with the delivery of meeting one of SOS	- role play and rehearsal of meeting 1 interaction	- peer review
6 th	To gain an	To be able to	To collect and interpret	Preparation of

November 2003	understanding of the relative status of statin prescribing in each allocated SOS practice	describe key characteristics of each nominated practice's statin prescribing	population level historical statin prescribing data (cost and volume) for allocated SOS practice, compared with the rest of the Glasgow practice population	brief summary of the status of the practice's statin prescribing and cost
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Examples of learning needs identified after critical appraisal and 1:1 discussion

Further learning need	Examples of potential sources of information
<p>1a. What would you say about the incidence and consequences of raised LFTs in the study?</p> <p>b. What would you advise practices to do in relation to LFTs in their population of HPS patients?</p> <p>c. What do the proposed new guidelines suggest for LFTs?</p> <p>2. How would you summarise the findings relating to incidence of muscle pain/weakness in the study and what would you conclude?</p> <p>3. Describe the patient groups and numbers of patients excluded from the study following attendance at the initial screening clinic visit.</p> <p>4. We thought there may be a 'Diabetes Subgroup Analysis' produced by the London Medicines Information Service. Can you source this?</p> <p>5. Could you clearly explain the concept of the placebo group having patients who also received simvastatin?</p> <p>6. In practice, assuming all else is equal, how many days of statin could a patient omit and still benefit as much as the patients in HPS?</p> <p>7. At a cellular level, what other effects do statins have, other than lipid lowering?</p> <p>8. Explain the term '95% CI' with reference to the study outcomes.</p> <p>9. What are the common adverse drug reactions associated with statins? Is there a dose-response relationship?</p> <p>10. What is the evidence for patients with a history of Coronary Artery Bypass Graft requiring cholesterol to be less than 4mmol/l? (Corollary: does this matter any more?)</p> <p>11. Please comment on the guidance given in the 'old' Glasgow guidelines for the secondary prevention of CHD in relation to</p> <ul style="list-style-type: none"> - doses of statins - age threshold - dietary advice <p>12. Can you confidently describe some basic features of each of the 3 previous secondary prevention studies (4S, CARE, LIPID)?</p> <p>13. What were the cut off points for LDL and total cholesterol levels in HPS?</p> <p>14. Describe how and where patient recruitment occurred?</p> <p>15. Could you explain Figure 7 to someone with a limited knowledge of the trial and statistical methods?</p> <p>16. What is a 95% Confidence Interval? How does it relate to p-</p>	<p>NNTs: Bandolier for general, EBM Online for statin trials.</p> <p>Confidence Intervals, p values: Master of Primary Care Statistics module lecture notes.</p> <p>Yusuf S. Two decades of progress in preventing vascular disease. The Lancet 2002;360:2-3.</p> <p>Law MR, Wald NJ, Rudnicka AR. Quantifying the effect of statins on</p>

<p>values?</p> <p>17. Please explain Relative and Absolute Risk reductions in relation to one of the trial outcomes.</p> <p>18. Explain the relevance of cholesterol level as an indicator of baseline vascular risk.</p> <p>19. Describe the incidence and clinical significance of dropout as a result of raised LFTs in the active and control groups.</p> <p>20. Describe the incidence and clinical significance of muscle enzyme problems.</p> <p>21. Explain ARR, RRR and NNT to a GP/Nurse who has limited understanding.</p> <p>22. Explain (with workings) how the following are different ways of describing the benefits/costs of a cardiac rehabilitation programme for heart attack victims:</p> <ul style="list-style-type: none"> -reducing the rate of deaths by 20% -producing an absolute reduction in deaths by 3% -increasing patients' survival rate from 84% to 87% -needing 31 people to enter the programme to avoid 1 death <p>23. What is your interpretation of the compliance issues raised by the study?</p> <p>24. Briefly summarise the details of previous primary (WOSCOPS, AFCaps/TEXcaps) and secondary prevention trials (CARE, 4S, LIPID).</p> <p>25. What would you say to convince a GP/Nurse that the beneficial effects of statins are additive to that of other secondary preventive drug strategies?</p>	<p>low density lipoprotein cholesterol, ischaemic heart disease and stroke: systematic review and meta-analysis. BMJ 2003; 326:1423-1436.</p>
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Problem Based Learning task (used in training day 3: 9th October 2003)

A 79 year old female (smoker, sedentary lifestyle) died suddenly last week. The cause of death was Myocardial Infarction. She had a past medical history of MI (2 years ago) and angina (3 years). Last recorded total cholesterol was 4.6mmol/l (1 year ago). Drug history: Aspirin, Nitrate, Statin (all taken for the past 3 years). ACE inhibitor (for the past 2 years).

Each of the five pairs of pharmacists was asked to find explanations for the following key features of the task:

- The short and long term pathophysiological processes potentially leading to the MI;
- Possible mechanisms contributing to the benefits of statin therapy;
- How and to what extent recognised risk factors contribute to the risk of suffering a vascular event;
- How to describe and quantify the combined benefits of statins, ACEs, Aspirin and Beta Blockers in decreasing the risk of a vascular event;
- What information to communicate to patients at risk, and how to communicate this risk.

Appendix XIV

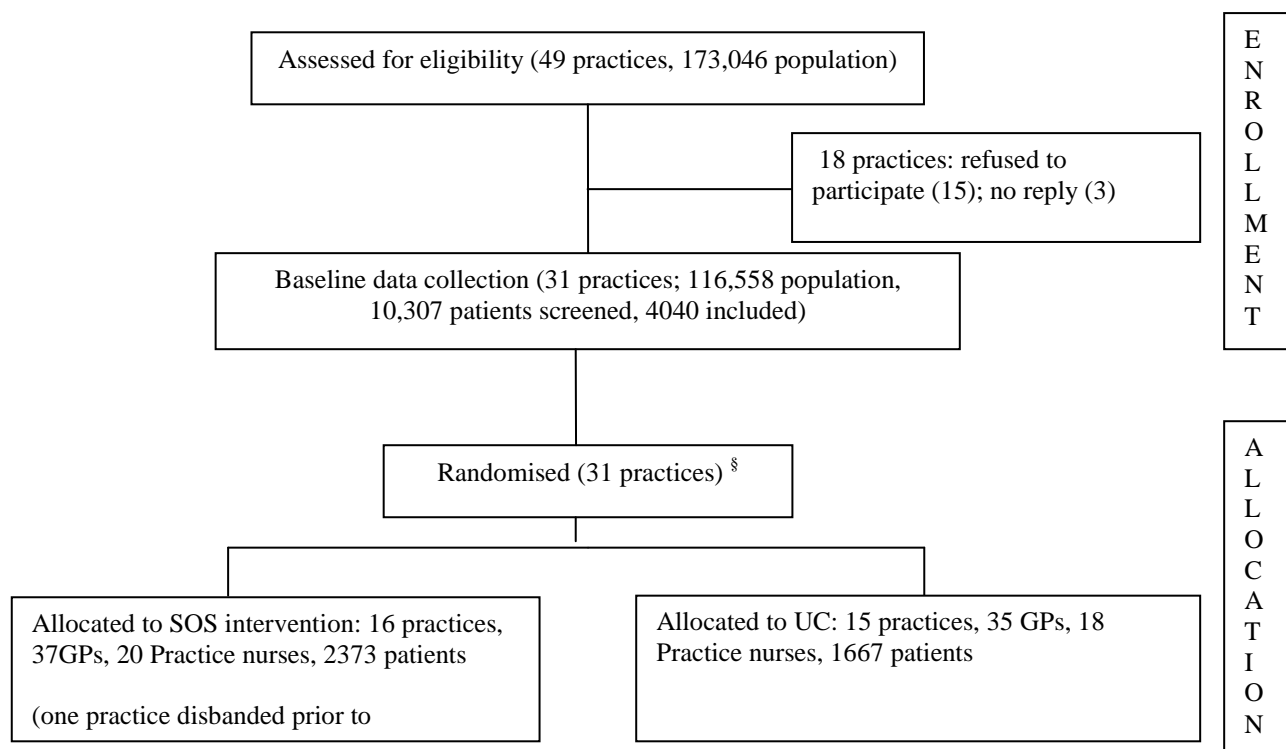
Duration of follow up by practice pairs

Group / Single Handed	Active / control	Pair	Duration of follow up for prescribing and cholesterol endpoints (yrs) †	Duration of follow up for vascular events detection (yrs) ‡
G	Active	1a	1.4	2.7
G	Control	1c		
G	Active	2a	1.7	2.7
G	Control	2c		
G	Active	3a	1.5	2.8
G	Control	3c		
G	Active	4a	1.8	2.6
G	Control	4c		
G	Active	5a	1.4	2.7
G	Control	5c		
G	Active	6a	2.1	2.7
G	Control	6c		
G	Active	7a	1.8	2.7
G	Control	7c		
G	Active	8a	1.4	2.3
G	Control	8c		
S	Control	1c	1.6	2
S	Active	1a§		
S	Active	2a	1.4	2.5
S	Control	2c		
S	Active	3a	1.7	2
S	Control	3c		
S	Active	4a	1.4	2
S	Control	4c		
S	Active	5a	2.2	2.8
S	Control	5c		
S	Active	6a	1.5	2.7
S	Control	6c		
S	Active	7a	2.2	2.7
S	Control	7c		
Mean (range)			1.7 (1.4 – 2.2)	2.5 (2 – 2.8)

† period between randomisation (4th November 2003) and earliest start date of follow up data collection in each pair of practices § Lost to follow up ‡ for patients traced from baseline to follow up

Appendix XV

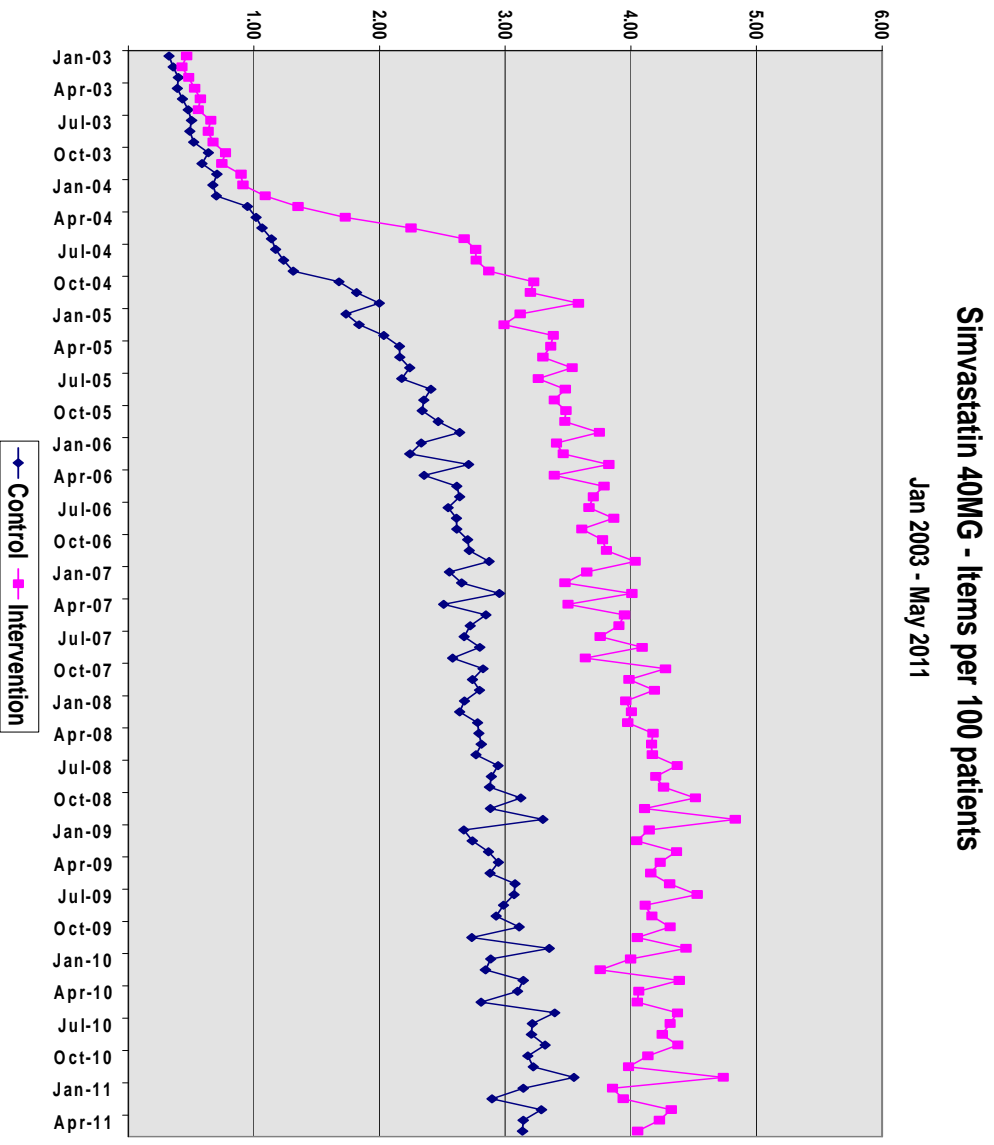
Practice and patient flow: enrolment and allocation



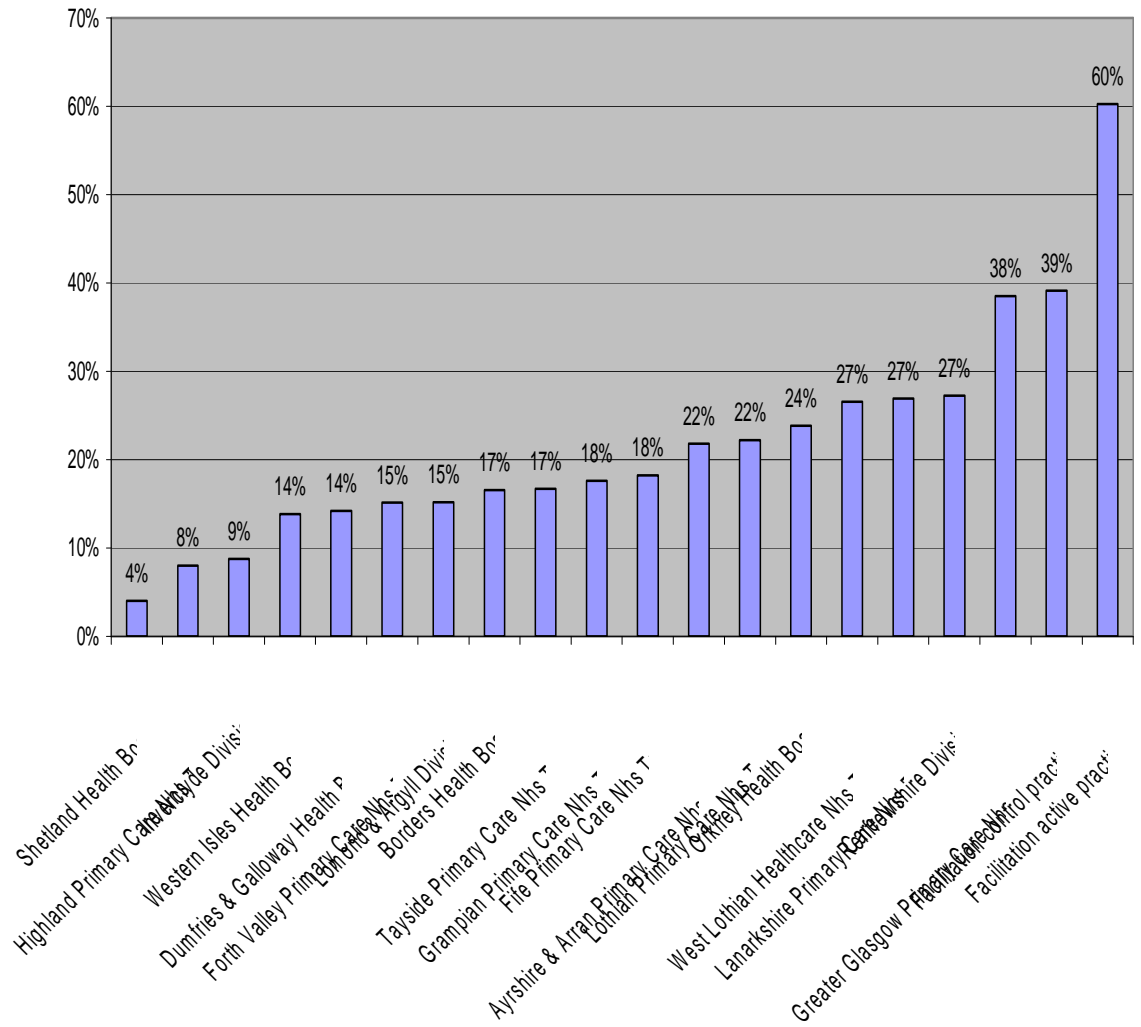
§ 1 practice (Single Handed) disbanded pre randomisation (unknown at time of randomisation)

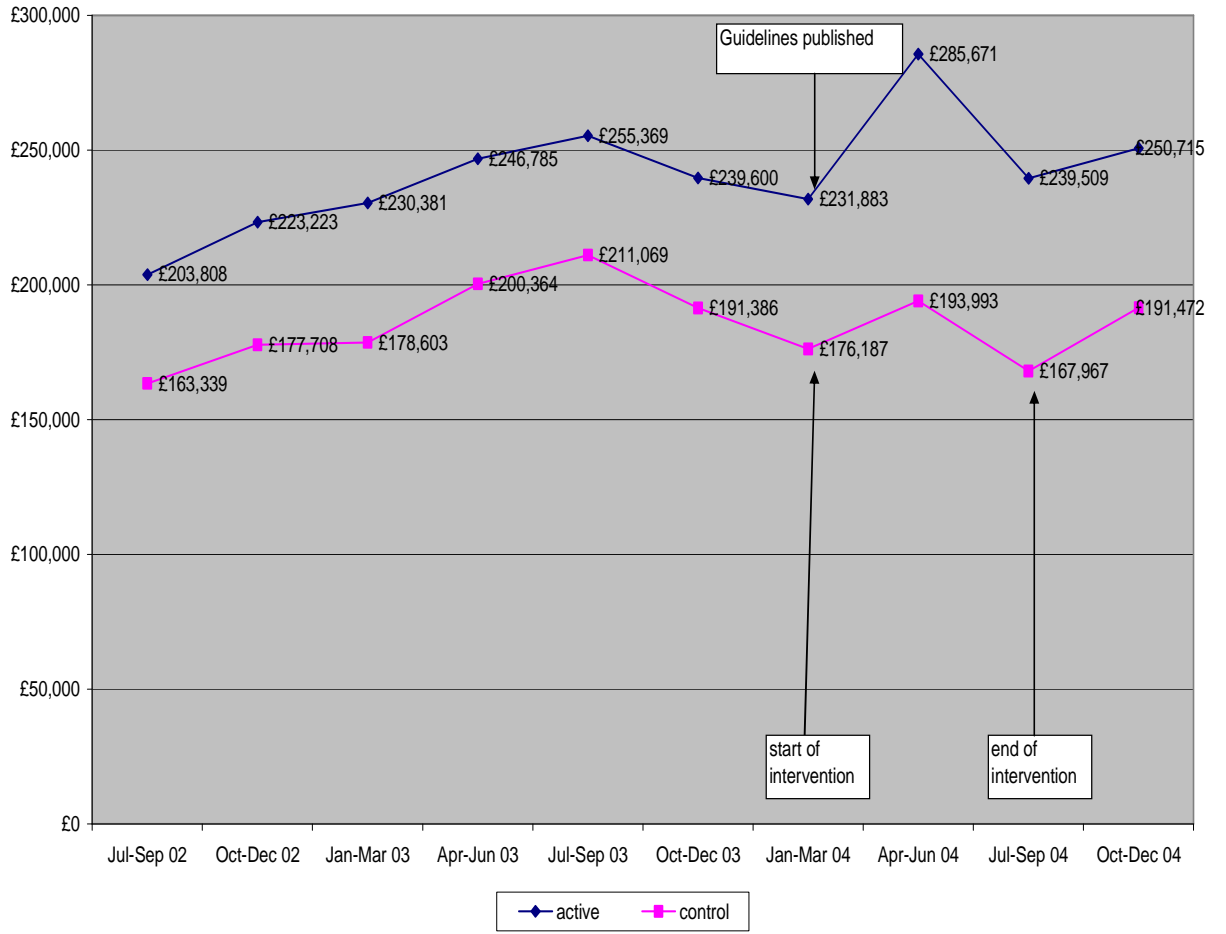
Appendix XVI

Simvastatin 40mg prescribing: SOS practices vs. UC



Simvastatin 40 as % of total statin items, Oct-Dec '04



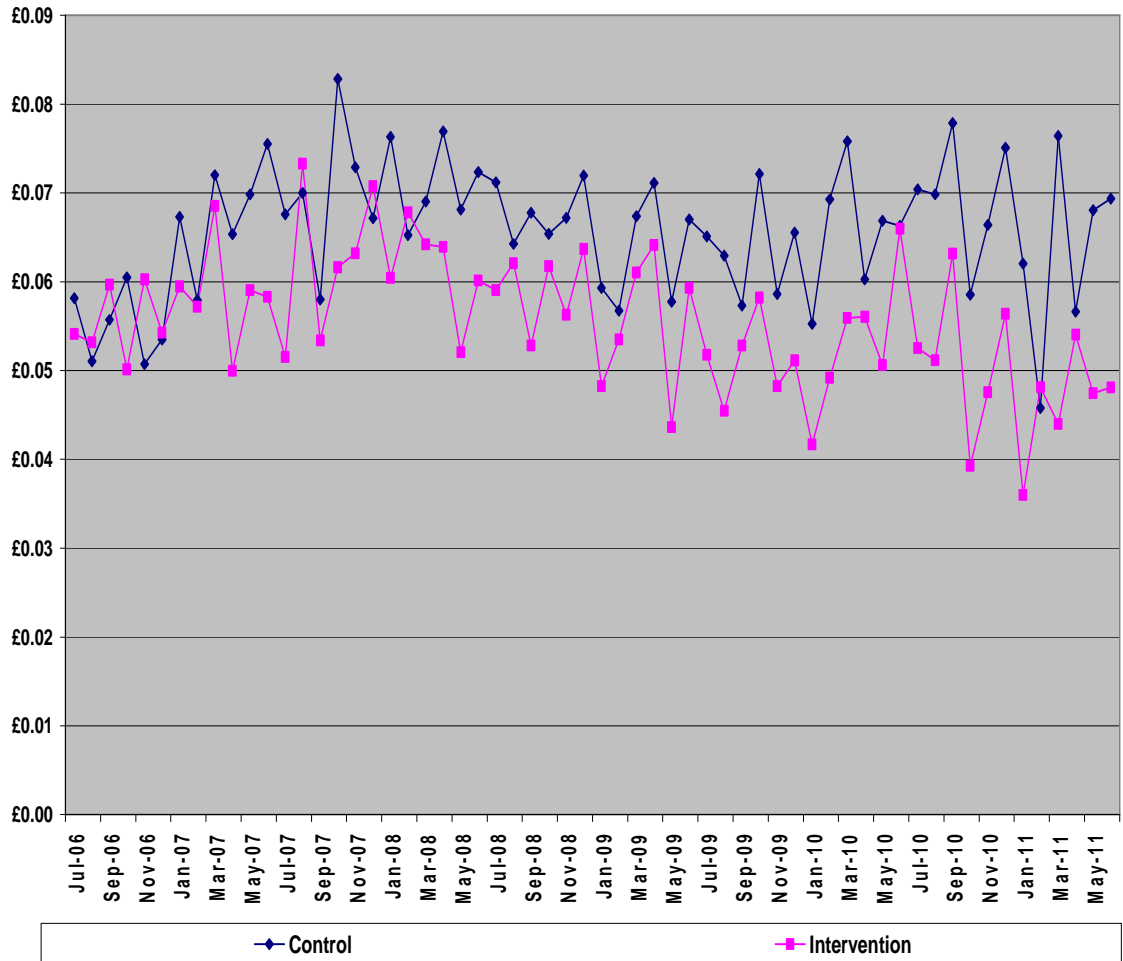


Appendix XVII

Non formulary statin prescribing: SOS vs. UC

Non-formulary Statins (Greater Glasgow Practices)

GIC per patient (July 2006 - June 2011)



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