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# **Use of primary care data for identifying individuals at risk of cardiovascular disease**

**Timothy Adrian Holt**

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**Health Sciences Research Institute**

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# Contents

	<b>Page</b>
<b>Contents</b>	<b>i</b>
<b>List of Abbreviations</b>	<b>xii</b>
<b>List of Tables and Figures</b>	<b>xiv</b>
<b>Acknowledgements</b>	<b>xviii</b>
<b>Declaration</b>	<b>xx</b>
<b>Abstract</b>	<b>xxiii</b>
<b>Chapter 1: Background and scope of the thesis</b>	<b>1</b>
1.1 Historical background	1
1.2 Relevance to current UK practice	5
1.3 What will be included and excluded	8
1.4 Existing evidence for reminder interventions	9
1.4.1 Existing systematic reviews	9
1.4.2 Summary of existing evidence	14
1.5 Chronology of the research	15
<b>Chapter 2: Cardiovascular risk prediction</b>	<b>26</b>
2.1 Introduction	26
2.2 Definitions and usage of ‘cardiovascular disease’ and ‘cardiovascular risk’	26
2.2.1 ICD-10 Classification	27
2.2.2 Read codes and SNOMED CT	28
2.2.3 Research study outcomes	29

2.2.4	<b>Sudden death from cardiovascular disease</b>	<b>32</b>
2.3	<b>Risk factors and their independence</b>	<b>33</b>
2.3.1	<b>Framingham risk factors</b>	<b>33</b>
2.3.2	<b>Definitions used by Framingham investigators and issues arising</b>	<b>33</b>
2.3.3	<b>More recent approaches</b>	<b>36</b>
2.4	<b>Absolute and relative risk</b>	<b>37</b>
2.5	<b>Missing data</b>	<b>38</b>
2.6	<b>Pre-treatment and modified risk factor values</b>	<b>39</b>
2.7	<b>Cardiovascular risk algorithms using alternative data to Framingham</b>	<b>42</b>
2.7.1	<b>MONICA</b>	<b>42</b>
2.7.2	<b>PROCAM</b>	<b>43</b>
2.7.3	<b>SCORE</b>	<b>43</b>
2.7.4	<b>QRISK and QRISK2</b>	<b>44</b>
2.7.5	<b>Comparisons between Framingham and alternatives</b>	<b>45</b>
2.8	<b>Alternative models for risk prediction</b>	<b>45</b>
2.8.1	<b>Basis for original and subsequent Framingham risk equations</b>	<b>46</b>
2.8.2	<b>Structure of more recent algorithms</b>	<b>49</b>
2.8.3	<b>Other possible risk models</b>	<b>50</b>
2.8.4	<b>Background to artificial neural networks</b>	<b>50</b>
2.8.5	<b>Published uses of ANNs for future CVD prediction</b>	<b>51</b>
2.8.6	<b>Advantages and disadvantages of ANNs</b>	<b>53</b>
2.9	<b>Summary</b>	<b>54</b>

<b>Chapter 3: Ethics of cardiovascular risk reduction</b>	<b>64</b>
3.1 Introduction	64
3.2 Ethics of disease prevention: ‘turning people into patients’	64
3.3 The ‘Rule of Rescue’	66
3.4 Individual choice versus population benefits	68
3.5 Patient decision making and informed consent	70
3.6 Absolute or relative cardiovascular risk?	72
3.7 Ageism and the ‘Fair Innings Argument’	72
3.8 Clinicians’ duty of care	74
3.9 Summary of ethical issues	75
<b>Chapter 4: Systematic literature review: Changing clinical practice through patient specific electronic reminders available in the consultation</b>	<b>79</b>
4.1 Introduction	79
4.2 Changing professional practice through electronic reminders	79
4.2.1 The Shojania 2009 review	80
4.3 Method for the systematic literature review	81
4.3.1 Protocol statement	81
4.3.2 Search strategies	81
4.4 Initial results	83
4.4.1 Decision rules	84
4.4.2 Initial examination of abstracts	85
4.4.3 Casting votes	86
4.4.4 Exclusions based on examining full texts and	

	<b>exclusion of non-controlled studies</b>	<b>86</b>
<b>4.5</b>	<b>Re-run of original searches</b>	<b>88</b>
<b>4.6</b>	<b>Results before final additions</b>	<b>90</b>
<b>4.7</b>	<b>Additions based on other systematic reviews</b>	<b>91</b>
	<b>4.7.1 Comparison with Shojania 2009</b>	<b>91</b>
	<b>4.7.2 Comparison with Kawamoto 2005</b>	<b>92</b>
<b>4.8</b>	<b>Final results</b>	<b>92</b>
	<b>4.8.1 Issues affecting interpretation</b>	<b>92</b>
<b>4.9</b>	<b>Data extraction</b>	<b>93</b>
<b>4.10</b>	<b>Narrative synthesis</b>	<b>98</b>
	<b>4.10.1 Methodological quality</b>	<b>98</b>
	<b>4.10.2 International issues</b>	<b>99</b>
	<b>4.10.3 Overall results</b>	<b>99</b>
<b>4.11</b>	<b>RevMan analysis</b>	<b>100</b>
	<b>4.11.1 Heterogeneity</b>	<b>101</b>
	<b>4.11.2 Random effects of a fixed effect?</b>	<b>101</b>
	<b>4.11.3 Subgroups of identified papers</b>	<b>102</b>
	<b>4.11.3.1 Binary outcomes versus continuous outcomes</b>	<b>103</b>
	<b>4.11.3.2 Process outcomes versus clinical outcomes</b>	<b>103</b>
	<b>4.11.3.3 Areas of care</b>	<b>103</b>
	<b>4.11.3.4 Unit of analysis</b>	<b>104</b>
	<b>4.11.4 Results of the process outcome studies</b>	<b>108</b>
	<b>4.11.5 Clinical outcome studies</b>	<b>109</b>
	<b>4.11.6 Comparability of studies</b>	<b>109</b>
	<b>4.11.7 Sensitivity analysis: exclusion of a study involving rare events</b>	<b>111</b>
	<b>4.11.8 Other studies included in the review but not in the RevMan analysis</b>	<b>111</b>

<b>4.12</b>	<b>Influence of excluded papers</b>	<b>112</b>
<b>4.13</b>	<b>Conclusions</b>	<b>112</b>
<b>Chapter 5: The e-Nudge trial: preparatory pilot work</b>		<b>120</b>
<b>5.1</b>	<b>Introduction</b>	<b>120</b>
<b>5.2</b>	<b>Identifying potentially at risk groups</b>	<b>120</b>
<b>5.3</b>	<b>The Newchurch experience</b>	<b>123</b>
<b>5.4</b>	<b>Original links with Egton Medical Information Systems (EMIS)</b>	<b>127</b>
<b>5.5</b>	<b>Developing links with local health care organisations</b>	<b>127</b>
<b>5.6</b>	<b>Funding for the trial</b>	<b>128</b>
<b>5.7</b>	<b>Ethical and R&amp;D approval</b>	<b>128</b>
<b>5.8</b>	<b>ISRCTN registration</b>	<b>129</b>
<b>5.9</b>	<b>Peer review</b>	<b>129</b>
<b>5.10</b>	<b>Summary</b>	<b>130</b>
<b>Chapter 6: Detailed methods for the e-Nudge trial</b>		<b>133</b>
<b>6.1</b>	<b>Introduction</b>	<b>133</b>
<b>6.2</b>	<b>Outline of the e-Nudge trial design</b>	
<b>6.2.1</b>	<b>Hypotheses</b>	<b>133</b>
<b>6.2.2</b>	<b>Setting</b>	<b>133</b>
<b>6.2.3</b>	<b>Participants</b>	<b>134</b>
<b>6.2.4</b>	<b>Intervention</b>	<b>134</b>
<b>6.2.5</b>	<b>Control condition</b>	<b>134</b>
<b>6.2.6</b>	<b>Outcomes</b>	<b>134</b>
<b>6.2.7</b>	<b>Duration of study</b>	<b>135</b>
<b>6.2.8</b>	<b>Analysis</b>	<b>135</b>

6.2.9	Quality assurance	135
6.3	The e-Nudge algorithm	135
6.3.1	Framingham algorithm	137
6.3.2	Groups identified by e-Nudge	138
6.3.3	Definitions	139
6.3.4	Changes to Group labels	142
6.4	The e-Nudge intervention	143
6.4.1	Screen reminders and lists	143
6.4.2	Amendments made to the wording of the e-Nudge alert messages	145
6.5	Outcome measures	146
6.6	Sample size calculation	146
6.6.1	Outline estimate of sample size required	146
6.6.2	Individual or cluster randomisation?	147
6.7	Recruitment	151
6.8	Randomisation and allocation concealment	152
6.9	Extracting and cleansing of outcome data	153
6.9.1	Primary outcome	153
6.9.2	Secondary outcomes	153
6.9.3	Quality assurance	154
6.9.4	Changes to the trial protocol	154
6.9.5	Statistical analysis and intention to treat	155
6.10	Summary	155
 <b>Chapter 7: Results of the e-Nudge trial</b>		<b>159</b>
7.1	Introduction	159
7.2	Practice recruitment and study population	159



7.2.1	Approaching practices	159
7.2.2	Revision of the sample size calculation	160
7.2.3	Age distribution	160
7.2.4	Deprivation and coronary heart disease standardised mortality ratios	162
7.3	Baseline characteristics of control and intervention arms	163
7.4	Trial denominator populations	165
7.5	Primary outcome: cardiovascular event rates	166
7.6	Secondary outcome measures: proportions in Groups A, B, C and D	167
7.7	Practice level changes in group proportions	169
7.8	Quality assurance sub-study	171
7.9	Intention to treat	172
7.10	Conclusions of the e-Nudge trial	173
<b>Chapter 8: The research process</b>		<b>175</b>
8.1	Introduction	175
8.2	Designing the e-Nudge software	176
8.2.1	The software platform	176
8.2.2	Choice of CVD risk algorithm	176
8.2.3	Programming the e-Nudge software	178
8.2.4	Randomisation mechanism	182
8.3	Troubleshooting the software	183
8.3.1	Performance testing the software ‘live’ in the test practice	183
8.3.2	Recording of fasting blood glucose results	191
8.3.3	Estimating the task of outcome data retrieval	193

<b>8.4</b>	<b>Issues affecting recruitment</b>	<b>195</b>
<b>8.5</b>	<b>Problems occurring during the trial</b>	<b>197</b>
<b>8.6</b>	<b>Changes to the protocol after commencing the trial</b>	<b>198</b>
	8.6.1 Shortening of the e-Nudge reminder messages	198
	8.6.2 Withdrawal of Group 1	199
	8.6.3 Withdrawal of Group 5	200
<b>8.7</b>	<b>The QRESEARCH survey</b>	<b>201</b>
	8.7.1 Survey sample	201
	8.7.2 Search strategies	202
	8.7.3 Rationale for the search strategies	202
<b>8.8</b>	<b>Collecting the trial results</b>	<b>204</b>
	8.8.1 Access to the Bureau system server	205
	8.8.2 Distinguishing new cardiovascular events from follow up entries	205
	8.8.3 Home grown codes and unwanted G6 codes	206
<b>8.9</b>	<b>Interviews with members of the public</b>	<b>207</b>
<b>8.10</b>	<b>Clinician interviews</b>	<b>208</b>
<b>8.11</b>	<b>Summary</b>	<b>208</b>
 <b>Chapter 9: Reflections on the completed research</b>		<b>211</b>
<b>9.1</b>	<b>Introduction</b>	<b>211</b>
<b>9.2</b>	<b>The systematic review</b>	<b>211</b>
<b>9.3</b>	<b>Realities of conducting primary care research</b>	<b>213</b>
<b>9.4</b>	<b>Design issues of the e-Nudge trial</b>	<b>214</b>
	9.4.1 Clustering and contamination	215
	9.4.2 Choice of primary and secondary outcome	217
	9.4.3 All events versus first events	217

<b>9.4.4</b>	<b>Imputation of missing risk factor values</b>	<b>219</b>
<b>9.5</b>	<b>Feedback from students</b>	<b>220</b>
<b>9.6</b>	<b>What would a revised e-Nudge trial design look like?</b>	<b>225</b>
<b>9.7</b>	<b>Summary</b>	<b>229</b>
 <b>Chapter 10: Outputs of the research</b>		<b>233</b>
<b>10.1</b>	<b>EMIS software for recognising undiagnosed diabetes</b>	<b>233</b>
<b>10.2</b>	<b>Advice to NICE on CVD risk estimation in primary care</b>	<b>235</b>
<b>10.3</b>	<b>e-Nudge as a software option in UK general practice</b>	<b>236</b>
<b>10.4</b>	<b>The EMIS Primary CVD Prevention Risk Assessment Toolkit</b>	<b>236</b>
<b>10.5</b>	<b>GE Healthcare searches</b>	<b>236</b>
<b>10.6</b>	<b>Publications and dissemination</b>	<b>237</b>
<b>10.7</b>	<b>Summary</b>	<b>238</b>
 <b>Chapter 11: Thesis summary and future research directions</b>		<b>241</b>
<b>11.1</b>	<b>Overall conclusions of the research</b>	<b>241</b>
<b>11.1.1</b>	<b>Two stage process of risk estimation</b>	<b>241</b>
<b>11.1.2</b>	<b>Adequacy of data</b>	<b>242</b>
<b>11.1.3</b>	<b>Impact of electronic reminders</b>	<b>242</b>
<b>11.1.4</b>	<b>Lay perspectives</b>	<b>243</b>
<b>11.1.5</b>	<b>Contextual basis for CVD risk estimation</b>	<b>243</b>
<b>11.1.6</b>	<b>Responsibility to act on identifiable at risk groups</b>	<b>244</b>
<b>11.2</b>	<b>Potential for development of the e-Nudge approach to other clinical areas</b>	<b>246</b>
<b>11.2.1</b>	<b>Algorithmic identification of at risk groups</b>	<b>246</b>
<b>11.2.2</b>	<b>Identifying risk of other conditions</b>	<b>247</b>

<b>11.3</b>	<b>Towards a nationwide adaptive prediction tool for cardiovascular disease prevention</b>	<b>249</b>
	<b>Bibliography</b>	<b>255</b>
	<b>Appendices</b>	<b>280</b>
<b>A.</b>	<b>Results of the Sheffield survey 1997 (referred to in Chapter 5)</b>	
<b>B.</b>	<b>Risk of bias table for systematic review</b>	
<b>C.</b>	<b>SQL program for the Framingham CVD equation</b>	
<b>D.</b>	<b>Invitation letter to practices for the e-Nudge trial</b>	
<b>E.</b>	<b>Practice letter of agreement form</b>	
<b>F.</b>	<b>The e-Nudge User's guide</b>	
<b>G.</b>	<b>Eight weekly email message sent to practices throughout the trial</b>	
<b>H.</b>	<b>Standard Operating Procedure for data collection</b>	
<b>I.</b>	<b>Data extraction form for systematic review</b>	
<b>J.</b>	<b>Patient invitation letter for interview project</b>	
<b>K.</b>	<b>Patient information leaflet for interview project</b>	
<b>L.</b>	<b>Patient consent form for in-depth interview</b>	
<b>M.</b>	<b>In-depth interviews with members of the public</b>	
<b>N.</b>	<b>Articles published prior to PhD registration</b>	
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## List of abbreviations

AF	Atrial fibrillation
ANN	Artificial Neural Network
AUROC	Area under the receiver operating characteristic curve
CDSS	Clinical Decision Support System
CEA	Cost effectiveness analysis
CHD	Coronary heart disease
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
CTV3	Clinical Terms Version 3 (Read codes)
CVD	Cardiovascular disease
ECG	Electrocardiograph
EMIS	Egton Medical Information Systems
EPOC	Effective Practice and Organisation of Care
FIA	Fair Innings Argument
GPRD	General Practice Research Database
ICD-10	International Classification of Diseases (version 10)
IT	Information technology
ITT	Intention to treat
LR	Logistic regression
LREC	Local Research Ethics Committee
LVH	Left ventricular hypertrophy
MeSH	Medical Subject Headings
MI	Myocardial Infarction
MIQUEST	Morbidity Information Query and Export Syntax

MONICA	Monitoring trends and determinants in cardiovascular disease
MQIC	Medical Quality Improvement Consortium
NPfIT	National Programme for Information Technology
NHS	National Health Service
PCT	Primary Care Trust
PRIMIS	Primary Care Information Service
PROCAM Study	Prospective Cardiovascular Munster Study
QALY	Quality adjusted life year
QMAS	Quality Management and Analysis System
QOF	Quality and outcomes framework
RR	Rule of rescue
SCORE project	Systematic Coronary Risk Evaluation project
SNOMED CT	Systematised Nomenclature of Medicine Clinical Terms
SNOMED RT	Systematised Nomenclature of Medicine Reference Terminology
SQL	Structured Query Language
TIA	Transient ischaemic attack
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organisation

<b>List of Tables</b>	<b>Page</b>
Table 4.1: Numbers of papers identified, and cumulative total from different source databases.	84
Table 4.2: Initial categories of decisions.	86
Table 4.3: Casting vote outcomes.	86
Table 4.4: Initial results of the re-run searches.	90
Table 4.5: Reasons for exclusion of 202 initial full papers examined.	91
Table 4.6: Outline of the 41 studies included in the systematic review.	94-97
Table 4.7: Heterogeneity values and odds ratios for all the binary outcome studies and for various subgroups of process outcome.	110
Table 5.1: Castle Medical Centre list size on 10.1.06	125
Table 5.2: Experimenting with my own Kenilworth practice's (anonymised) data remotely from Newchurch's Teddington data warehouse on 10.1.06.	125
Table 6.1: A range of possible values for the intra-class correlation co-efficient and their implications for the e-Nudge sample required based on m=111.	149
Table 7.1: Numbers of patients in age groups 50-75 years and over 75 in	



each practice.	161
Table 7.2: Deprivation indices for the super output areas of the trial practices and Coronary Heart Disease indirectly standardised mortality ratios (based on ICD-10 I20-I25).	163
Table 7.3: Numbers identified and proportions of the over-50 year population in each Group at baseline.	165
Table 7.4: Denominator population values during the e-Nudge trial.	166
Table 7.5: Cardiovascular event rates in the two arms of the trial.	167
Table 7.6: Group proportions in the baseline and outcome populations by trial arm.	168
Table 7.7: Intervention patients identified as proportion of the over 50 year population at baseline and after two years in the eighteen practices that completed the trial for groups A and B.	170
Table 8.1: Initial Group proportion results at the test practice on 5.5.06.	184
Table 8.2: Characteristics of a sample of Group 2 individuals identified on 5.5.06.	187
Table 8.3: Numbers identified in the test practice on 9.5.06.	189
Table 8.4: Numbers of patients at the test practice identified with two	

Read codes present in their record between 1.1.04 and 1.1.06.	191
Table 9.1: List of factors identified by Mayo-Smith and Agrawal in the published literature potentially determining effectiveness of computerised reminders (CRs).	227-228

## List of Figures

Figure 4.1: Forest plot of the two studies reporting a clinical outcome.	105
Figure 4.2: Forest plot of all studies reporting process outcomes, including either population or reminder opportunity denominator, grouped by area of care.	106
Figure 4.3: Forest plot of all studies using the reminder opportunity as the unit of analysis.	107
Figure 4.4: Forest plot of all studies using a population level denominator as the outcome.	107
Figure 6.1: Identification of Groups 1-4.	141
Figure 6.2: Identification of Group 5.	141
Figure 6.3: Identification of Group 6	142

Figure 6.4: Crude prevalence (columns) and indirectly standardised prevalence ratios (joined points) for Coronary Heart Disease and Stroke/TIA among the 36 practices of South Warwickshire in March 2005. 151

Figure 7.1: Numbers of registered patients identified 50-74 years and over 75 years in each practice. 161

Figure 7.2: Age structure of the study population and background UK population. 162

Figure 8.1: Four components of the Anderson 1991 Framingham algorithm. 179

## **Box**

Box (Chapter 6): Definition of a cardiovascular event. 146

Box (Chapter 7): Example of how the e-Nudge helped a practice identify patients for CVD risk reduction. 171

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## Declaration

I declare that none of this work has been submitted for a degree at another university.

The preparation of this thesis manuscript was entirely my own work, but I have benefitted from the comments and suggestions of my supervisors on earlier drafts.

The e-Nudge trial was a randomised controlled trial that I led as Principal Investigator. My supervisors Professor Margaret Thorogood and Dr Frances Griffiths had input into the trial's design. I led on the design of the e-Nudge software, which was programmed by Dr David Stables of EMIS. I was responsible for all communications with participating practices throughout the trial. Correction of software problems was achieved through collaboration between me and David Stables. Dr Tim Friede advised on the analysis of the outcome data and other co-authors contributed to the drafting of the published articles that resulted from the research.

The Systematic literature review described in chapter 4 was a collaborative piece of research that I led. Inclusion and exclusion decisions were shared between me and my supervisors. I analysed the included papers using RevMan software.

The topic guide for the interviews with members of the public was developed through discussion with my supervisors. I recruited the participants, conducted the interviews, arranged for transcription of the audio-taped data, and carried out the thematic analysis myself.

The QRESEARCH project was a collaborative effort involving all five co-authors of the published report. I led on the drafting and submission of the completed paper. Julia Hippisley-Cox was the guardian of the data and carried out the searches from the University of Nottingham.

## **Publications**

Two publications describe preparatory work and ideas relevant to this research but were published before I registered for PhD study. These are listed as references 1-2 below.

Publications arising directly from the PhD research and published before thesis submission are listed below as references 3-8.

The final report of the e-Nudge trial has been accepted by the *British Journal of General Practice* but will not be published before thesis submission. A book '*ABC of Diabetes(6<sup>th</sup> Edition)*' is also due to be published early in 2010 by Wiley-Blackwell and refers to the work published in reference 7.

I am also intending to submit for publication (with Margaret Thorogood and Frances Griffiths) the Systematic literature review. This manuscript is currently still in preparation.

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## Abstract

The aim of this research was to explore the potential of routinely collected primary care data to support the identification of individuals for cardiovascular risk reduction. The work involved a systematic literature review of reminder interventions operating at the point of care; a randomised controlled trial of a novel software tool to facilitate the targeting of individuals at risk of cardiovascular disease; and an exploration of qualitative issues relevant to the challenge of cardiovascular risk reduction in current practice.

The Systematic review resulted in a narrative synthesis and a meta-analysis. It concluded that reminder interventions are generally effective at changing practitioner behaviour, but the effect is inconsistent, probably dependent on organisational context, and difficult to predict.

The e-Nudge trial involved 19 practices in Coventry and Warwickshire, who used the e-Nudge software tool for two years. This tool was programmed for the project by the clinical software company EMIS. Whilst the primary outcome (cardiovascular event rate) was not significantly reduced in this timescale, a beneficial effect was demonstrated on the adequacy of data to support risk estimation and on the visibility of the at risk population. A new means of addressing the problem of undiagnosed and late-diagnosed diabetes was also discovered.

Qualitative aspects of this area of care are presented through a discussion of ethical issues, a limited series of interviews with members of the public included in the appendix, and extensive field notes taken throughout the research. These provide some context in support of the e-Nudge trial.

Routinely collected data of UK general practice provide a potentially rich resource to support primary cardiovascular disease prevention, but practical, ethical and conceptual issues must all be addressed to optimise their impact. This conclusion forms the thesis to be explored and justified through this dissertation.

# Chapter 1: Background and scope of the thesis

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## 1.1 Historical background

The development of National Health Service (NHS) software infrastructure during the last two decades of the 20<sup>th</sup> Century created new opportunities to exploit the availability of health information. This applied particularly to primary care through the creation of electronic health records in the late 1980s. Standardisation of coding (i.e. the shared use of a defined set of electronic codes for clinical and administrative data), and the requirement that independent clinical software companies adhere to interoperability standards defined by *Health Level 7* (1) allowed this infrastructure to develop in a cohesive way. The research described in this thesis made use of, and required this standardised infrastructure.

An ambitious agenda for NHS integration was proposed in 1998 by the *National Programme for IT* (NPFIT) and is summarised in the document *Information for Health* (2). This provided a vision for NHS software development with three major components: electronic prescribing, on-line transmission of records from practice to practice and, perhaps most significantly, the NHS Care Records Service (CRS), through which individual records could be accessed from outside the practice. The subsequent failure of this vision to meet its own expected deadlines is beyond the scope of this work, and the concept of a fully integrated NHS software environment still faces seemingly insurmountable barriers. However, standardisation of data coding and the integration of previously unconnected domains (such as those of hospital laboratories and primary care records) succeeded in achieving the necessary interoperability to support the *Quality and Outcomes Framework* of the new General Medical Services Contract of 2004 (3). This required QMAS (Quality Management and Analysis System) (4) software that extracts relevant data anonymously from practices to monitor

performance remotely against QOF targets. This development moved chronic disease management away from individual patient care at the practice level, and closer to a nationally distributed public health endeavour.

From a research perspective, routinely collected primary care data were a potentially rich but problematic resource from an early stage (5). Data began to be extracted from multiple sites into the *General Practice Research Database* (GPRD) as early as 1987 (6), and this usage increased during the following two decades. Information on clinical data, including health variables, events, prescribing, referrals, and demographic profiles were pooled and made available to the research community. This led on to a range of data repositories and integrated data collection systems summarised by Gnani and Majeed (7). In addition to GPRD and QMAS, they include MIQUEST (Morbidity Information Query and Export Syntax) (8), Prescribing Analysis and Cost (PACT) data (9), the RCGP Weekly Returns Service (10), the Primary Care Information Service (PRIMIS) (11), and QRESEARCH, a large database hosted at the University of Nottingham (12). But at the outset of GPRD in the late 1980s, such health data were still recorded inconsistently. Standardisation of data coding came later, during the 1990s and 2000s, for a number of identifiable reasons.

Electronic data recording was, at the start of the 1990s largely designed to support individual care. It then expanded to meet the needs of clinical audit, later becoming a tool for monitoring adequacy of care at the practice level and of comparing different practices by primary care organisations. These included Health Authorities, Health Boards, Primary Care Groups and later Primary Care Trusts who were able not only to extract anonymised data remotely (as GPRD already could) but also to feed the results back to practices on a regular basis. This process required a certain level of code standardisation that was unnecessary for the requirements of the decade before. A further early incentive for standardisation of electronic coding was in the area of prescribing. Electronic coding facilitated the monitoring of drug usage and expenditure, compliance, identification of adverse reactions, and the monitoring of prescribing

behaviour of clinicians and practices. As a significant minority of practices also function as dispensing pharmacies managed as businesses by general practitioners, the benefits of electronic coding became increasingly evident, and even more likely to spill over into clinical care.

The use of electronic databases for quality assurance provided an unprecedented opportunity to identify adverse drug reactions and other safety issues, areas exploited early on by GPRD, attracting investment from the pharmaceutical industry.

Another major trigger was the introduction of clinical audit, a requirement of all NHS clinicians identified in the 1989 White Paper '*Working for Patients*' (13) and in the subsequent General Medical Services Contract of 1990. Whilst addressed to the NHS as a whole, this move was designed to increase the accountability of general practitioners as the key 'gatekeepers' of NHS expenditure (14). This set the scene for *Fundholding*, a contractual system that controlled referral and prescribing behaviour as well as secondary care commissioning during the mid-1990s (15). Although response to the introduction of audit was mixed (16), the early 1990s saw a proliferation of audit activities at the practice level, through which a clinical area (such as hypertension) would be examined and subjected to the clinical audit cycle. A list of patients whose most recent blood pressure was out of a predefined target range could be produced only if the data were coded consistently. This provided an incentive for the recording of blood pressure measurements using electronic codes rather than as free hand entries. Clinical software providers facilitated this process through automated screen templates, which rapidly developed for all the chronic diseases that were increasingly managed in primary care during this time.

Central to this process was the concept of a 'disease register.' Outside the primary care environment, the benefits of disease registers are less evident. But where (in principle) each resident in the population is identifiable through a unique identifier (the NHS number) and registered with one (and only one) general practice, the disease

register provides the means of attributing responsibility of care to named clinicians or practices. Cross-referencing above the practice level using NHS numbers developed during the 1990s. At the start of this decade, it was common for practice lists to include ‘ghost’ patients – individuals who were still registered after they had left the area and re-registered with a new practice elsewhere. Capitation payments could be made concurrently to more than one practice for the same patient. The cross-checking made possible by centralised data on NHS numbers has reduced this duplication, with the result (in principle) that each practice now has sole responsibility for all their registered patients (even if they commission care from elsewhere). Disease registers have become the focus of structured, systematic chronic disease management in primary care. More recent moves to diversify primary care provision are justified on various bases including the need to reduce health inequalities (17), but might in principle undermine this achievement.

Electronic recording of diagnoses combined with clinical software search engines together facilitated the *automated* creation of disease registers. Before the advent of electronic records, such registers (if they existed at all) were created using ‘hard copy’ systems that required an active initiative on the part of clinician or administrative staff to record and maintain the information on card files. This also applied to Age/Sex registers, regarded until quite recently a minimum standard of demographic record keeping in general practice. Following the introduction of electronic records and recognised codes for disease and other categories, registers were created automatically as soon as practice staff recorded such information in searchable form. Producing a ‘register’ of patients with a certain condition became almost trivially easy using a simple search on the appropriate codes, although the maintenance of disease registers for conditions (unlike cardiovascular disease) that may resolve and become a past problem is a non-trivial issue relevant to this work to be discussed in Chapter 6.

In many important clinical areas (e.g. autism, osteoporosis, peripheral vascular disease, learning difficulties, HIV infection, psoriasis) the ‘register’ may be a poor reflection of the true prevalence of the condition in the community, whilst for others (such as stroke or coronary heart disease) it has become increasingly adequate as a result of the developments described above. The standardised coding of such information has become important in the establishment of meaningful primary care disease registers and following on from this the development of well organised, proactive care.

## **1.2 Relevance to current UK practice**

Integrated software infrastructure is still a fairly recent development, but in addition to the potential benefits discussed above (e.g. monitoring of prescribing, safety, quality assurance, and contracting), the availability of integrated information provides for a more efficient system of *targeting* interventions towards the neediest individuals. This approach potentially benefits recipients, providers and commissioners. Identifying *at risk* individuals or groups using health data, including practice based data collected during routine care, increases the efficiency of this process, because the effectiveness of preventive interventions is generally greatest when aimed at those at highest risk. This specific issue is the focus of this thesis, applied to the areas of cardiovascular and diabetes risk reduction.

From the advent of electronic records, cardiovascular disease data were generally well supported by the Read coding system discussed in the next chapter. For each risk factor, an appropriate Read code is usually available and there is often a selection of alternative codes with similar meanings. For other conditions, where relevant Read codes did not exist, the facility was available for practices to create their own electronic codes. This enabled primary care teams to undertake audits of practice specific activities for which no relevant Read code existed. During the latter half of the

1990s this practice began to be discouraged as the NHS prepared for integration above the practice level. Such 'home-grown' codes might be meaningless when retrieved outside the original practice context and so were seen as a barrier to standardisation and data integration. The most recent development in this process has been the Directed Enhanced Service (DES) for Information Management and Technology of 2008, through which practices rationalised their use of such codes. In 2002, a new international coding system SNOMED CT (Systematised Nomenclature of Medicine Clinical Terms) was created through a merger of the Clinical Terms Version 3 (a subgroup of Read codes used in the NHS) with the SNOMED RT (Reference Terminology) system (18), the latter already in use by the College of American Pathologists (19). This expanded system is becoming increasingly adopted into the NHS and is the basis for the new EMIS-Web electronic record system to be discussed at the end of this thesis. It is designed to support the integration of health data at an international level.

Practice based audit activity led on later in the 1990s to Primary Care Organisations (PCOs) carrying out audits remotely and providing comparisons with similar practices in the region, adjusted for demographic confounders such as age and deprivation distributions. This was only possible if appropriate data were standardised across practices in the region under study. Before long, this concept applied to the NHS as a whole.

The focus on cardiovascular disease contrasts with that of other medical conditions including malignancy, whose risk factors or symptom profiles (particularly with regard to electronically coded data) are often still poorly defined at least in such a way that would facilitate early detection (20). Social health variables are poorly recorded in primary care. Even a factor as important for cardiovascular outcomes as ethnicity has only very recently started to be recorded systematically by practices. Risk factor information is often incomplete, and its adequacy for cardiovascular disease will be explored later in this thesis. There are many problems in health care that require

identification and targeting of those at greatest risk, as suggested above. Of these, cardiovascular disease has several advantages as a topic for primary care research.

Firstly, cardiovascular risk variables have benefited above all others in the data standardisation process described above. Prior to the Quality and Outcomes Framework, other initiatives provided incentives (including financial) for the collection of cardiovascular risk factor information. This particularly applied to the 'Banding' system of the early 1990s, through which practices would collect data on such variables as smoking status, blood pressure, and cholesterol levels. Different levels of activity ('Bands') would attract different levels of payment. This system was later dissolved, but the resulting electronic data were saved in the practice systems, available for future access. The result of this was that by the end of this decade a tradition had become established to promote cardiovascular risk factor recording in coded, standardised form.

Secondly, cardiovascular risk is a well researched area and the relative importance of the various risk factors is known quite well, as a result of several large cohort studies and epidemiological surveys to be discussed in Chapter 2. The result of this is that risk algorithms that weight the main independent factors and produce risk estimates, are widely available and in common use among primary care practitioners all over the UK. Targeting patients at raised cardiovascular risk has become an area of intense interest over the past few years, because of the availability of these algorithms and of the opportunity to modify risk through a variety of interventions.

Finally, the study of cardiovascular risk benefits from the fact that the outcomes (cardiovascular events) are to a large extent recorded electronically in the same databases as the risk factor data. The same is not true of outcomes such as hospital admission, which may occur without any coded entry into the practice based record, or of fall risk, where the fall itself might (occasionally) be recorded in primary care but the risk data (such as whether there are stairs at home, whether the patient uses a walking aid) are, if recorded at all, more likely to be found in a database at social



services, at a local occupational therapy provider, or in housing data of the local council.

The importance of cardiovascular risk reduction to current UK practice is reflected in its inclusion in a number of recent guidelines and recommendations by expert bodies. These include the National Framework for Coronary Heart Disease of 2000 (21), the Fourth report of the British Hypertension Society of 2004 (22), the Second report of the Joint British Societies on prevention of cardiovascular disease in clinical practice of 2005 (23), the NICE Technology Appraisal 24: Statins for prevention of cardiovascular events of 2006 (24), the SIGN Clinical Guideline 97: Risk estimation and the prevention of cardiovascular disease of 2007 (25) and the NICE Clinical Guideline 67: Lipid Modification of 2008 (26). All of these documents recommend the identification of individuals for preventive interventions based on estimated cardiovascular risk, generally drawing on the availability of standardised risk factor data in UK general practice.

### **1.3 What will be included and excluded**

This research concerns the use of general practice data for identifying ‘at risk’ individuals for cardiovascular disease. Whilst not explicitly stated in the title, in the current environment this effectively means electronic, rather than paper based data. The work is exclusively NHS based, and draws on a collaborative relationship with EMIS, one of the UK’s suppliers of clinical software to general practice, and (to a much smaller degree) Newchurch, a private company providing information technology solutions under contract with the NHS. EMIS is one of a number of clinical software suppliers in the UK, so throughout the thesis I will take care to focus on issues that are common to all systems rather than ‘EMIS-specific.’

## **1.4 Existing evidence for reminder interventions**

The major issues to be investigated through this research involved the adequacy of electronic data to support a targeted programme of CVD risk reduction in primary care, and the role of automated reminders to influence clinical practice. At the outset, I looked for evidence that this work had already been done or was in process. As well as a number of completed published reviews, a listed Cochrane protocol was entitled ‘On-screen computer reminders: effects on professional practice and health care outcomes’ by Richard Gordon, Jeremy Grimshaw, Martin Eccles, Rachel Rowe and Jeremy Wyatt (27). I contacted Jeremy Grimshaw at the University of Ottawa and Martin Eccles at the University of Newcastle, who advised me that publication was expected fairly soon. I was told that the lead author was now Kaveh Shojania, whom I then also contacted. He gave me an update and again suggested an early publication date. He also sent me 38 relevant citations that his group were considering. I expected that this review would overlap significantly with my area, but when I studied the protocol I realised that there were some significant differences. Most importantly, I was interested in reminders generated by *patient specific data*, rather than computerised decision support or other guidelines that were only condition or medication specific.

### **1.4.1 Existing systematic reviews**

In addition to this protocol (and the completed review that followed discussed in Chapter 4), I found 18 published reviews. Some of these were conducted systematically and others less formally. As they were not contributing original data they were not included in my own review (conducted in collaboration with my supervisors and described in Chapter 4), but were nevertheless useful sources of information for the thesis. None were sufficiently recent or relevant to my work to make our review unnecessary. Some included a range of process interventions that targeted patients as well as providers, and in many of them computerised reminders were just one

intervention among several included in the review. The following paragraphs describe some key insights arising from these papers.

Balas et al (1996) (28) reviewed 98 randomised controlled trials of clinical information systems. This was a comprehensive review, but only 64% of the interventions targeted the health care provider and this review is no longer very recent. Provider reminders were generally found to make a significant difference to process outcomes.

Balas et al (2004) (29) described forty studies of computerised knowledge management interventions to support diabetes care. These included eight studies of the effects on guideline compliance of computerised prompting, reporting significantly improved compliance in six of them.

Bennett, Glasziou and Sim (30) reviewed articles specifically related to medication management, concluding that computerised reminders and feedback were generally valuable in this situation.

Berlin, Sorani and Sim (31) used a previously developed taxonomy of computer-based clinical decision support systems (CDSSs) to describe the current literature. Seventy-four CDSSs were reported in fifty-eight studies, and two distinct subsets were identified: those aimed at patients (via mail or telephone) and online systems directed at physicians in inpatient contexts. These studies were generally not relevant to my current work, but an important conclusion was derived: that CDSSs are heterogenous and dependent on the clinical or workflow setting, limiting their generalisability.

Garg et al (32) reviewed 100 controlled trials of CDSSs both to investigate their effectiveness and to identify features predicting success. They found that the quality of the trials improved over time, and that improvements in practitioner performance were more evident than patient outcomes. Out of 21 trials of reminder systems, 16 produced positive benefits in terms of performance. Automatic prompts were generally more effective than those requiring the user to activate them.

Hasman, Safran and Takeda (33) concluded that reminder systems linked to physician order entry systems were generally beneficial but their use for diagnostic support was more limited.

Kawamoto et al (34) studied 70 articles describing CDSSs and undertook regression analyses to determine the influence of up to fifteen characteristics of the intervention predictive of success in terms of improved clinical practice. Four features produced independent predictors. These were:

- Automatic provision of decision support as part of clinical workflow
- Provisions of recommendations rather than just assessments
- Provision of decision support at the time and location of decision making
- Computer based decision support

Thirty out of 32 papers that included all four features significantly improved clinical practice. This suggests the need to embed such interventions into the working environment at the point of care.

A review by Kupets and Covens from 1966 to 2000 (35) identified papers related specifically to improving breast and cervical cancer screening using a variety of techniques. They identified three categories of intervention: physician based, physician/patient based, and patient based. The physician based strategies such as manual and computer generated reminders proved the most effective at improving screening rates. They described the concept of a 'Number Needed to Intervene' (NNI), and estimated that in the case of reminder notices 3 physicians need to be exposed to the intervention for one of them to order a screening test. This number was lower (i.e. more effective) than for other types of intervention.

McPhee and Detmer (36) also reviewed approaches to the problem of cancer screening using office based interventions. This review was published in 1993 and so is now rather out of date when considering the computerised examples. Of relevance to

my own review described below, the authors drew a distinction not only between physician and patient directed interventions (and both), but also between ‘in-reach’ and ‘out-reach’ activities. In-reach approaches include the consultation based reminders that are of particular relevance to the e-Nudge trial, although other examples included practice based audit which was excluded from our own review. The conclusion of this review was generally positive regarding the effectiveness of office based interventions for cancer prevention.

Mitchell and Sullivan (37) considered more generally the impact of computers in primary care consultations. They identified ‘a descriptive feast but an evaluative famine,’ highlighting the relative lack of high quality, controlled trials of computerised interventions, in contrast to the volume of papers describing interventions, their development, use and acceptability. Out of 89 papers included, 61 reported the effect of computers on practitioner performance, 17 used patient outcomes, and 20 were qualitative studies of practitioner and patient attitudes. This review identified negative aspects related to process measures (including lengthening consultations) but not to patient outcomes. The phenomenon through which effectiveness may fall after withdrawal of the intervention was also identified.

Montgomery and Fahey’s review (38) included 7 randomised controlled trials investigating the use of computers specifically in the area of hypertension management. These studies included 11962 patients and were combined using a narrative rather than meta-analytical approach due to heterogeneity of patient populations, interventions and outcomes, although their methodological quality was similar. A beneficial effect was seen on processes of care such as follow up, but once again the effects on patient outcomes (such as control of blood pressure) were less conclusive.

A meta-analytical approach was, however possible in a review of general practitioner based reminders to support cervical cancer screening reported by Pirkis, Jolley and Dunt (39). Ten studies were identified and a positive effect demonstrated on

a woman's chance of having a Pap smear if the GP had been reminded. A strong recommendation over the use of such reminders was made.

Shea, DuMouchel and Bahamonde (40) conducted a meta-analysis of 16 randomised controlled trials reporting the impact of computerised reminders in six areas of preventive care (vaccinations, breast cancer screening, colorectal cancer screening, cardiovascular risk reduction, cervical cancer screening, and 'other preventive care.'). The first four of these areas were associated with benefits of the reminders but not the final two. Ten out of the sixteen interventions evaluated were directed at physicians, the remainder at patients or family. Cardiovascular preventive activities included measurement of blood pressure; follow up of hypertension; cholesterol screening; and dietary assessment and counselling. The overall odds ratio (ratio of odds of completing the target behaviour in intervention and comparator arms) was 1.77 [95% CI 1.38-2.27], and for the cardiovascular risk reduction subgroup 2.01 [95% CI 1.55-2.61].

Shiffman, Liaw, Brandt and Corb (41) reviewed studies of computer based interventions including clinical guideline implementation systems and their impact on clinician behaviour and patient outcomes. Quantitative meta-analysis was impossible due to study heterogeneity. A narrative synthesis concluded that better control of confounding factors would be needed to derive firm conclusions over the effectiveness of such systems at influencing clinician behaviour. Seventeen out of twenty systems described used paper based reminders, albeit computer generated. The authors remarked that 'the paperless office remains a vision of the future.'

Shojania 2006 (42) (note different from Shojania 2009 discussed in Chapter 4) considered only interventions related to diabetes care and using glycosylated haemoglobin level as the outcome, but included any type of quality improvement strategy. Studies using before/after designs were included as well as randomised and quasi-randomised trials. Out of eleven strategies, team changes and case management interventions produced the clearest benefits. Publication bias (suggested through the

finding of more clearly positive outcomes in the smaller studies) was an issue, and the authors also commented on the difficulties in classifying the complex interventions involved in quality improvement when assessing effectiveness.

Tu and Davis (43) reviewed the evidence for educational interventions in the management of hypertension. Reminder systems were only one of a number of interventions that were generally not relevant to my research, including academic detailing, but were apparently the most promising in terms of changing clinician behaviour. However, once again it was the processes of care (such as follow up) rather than clinical outcomes (such as blood pressure levels) that benefited.

van der Sijs et al (44) identified 17 papers describing trials of drug safety alert systems used during computerised order entry. This review was concerned largely with the reasons why physicians over-ride such alerts (in 49%-96% of cases) rather than their effectiveness. Problems include low specificity or sensitivity, unclear information content, and incorrect handling of the alerts. This review is important because it emphasises the need to embed a new intervention such as an alert system in the workflow context if it is to be useful rather than disruptive.

Finally, Dexheimer et al (45) updated a previous review by Balas et al (2000) (46) of both paper-based and computerised prompts related to preventive measures. Reporting nine years later than Shiffman et al (discussed above), they also found a preponderance of paper based rather than fully computerised systems, the latter involved in just 8 out the total of 61 studies. They found an increase in preventive care measures of between 12% and 14% averaged over all studies. Cardiac care and smoking reminders were the most effective.

#### **1.4.2 Summary of existing evidence**

In summary, the existing systematic reviews discussed above provided a range of insights that influenced my own research, and can be distilled under the following headings:

- Reminder systems are complex interventions that may influence more than one component of the health care environment: practitioners, patients, administrative staff, and workflow.
- Reminder systems lend themselves well to computerisation, but this does not automatically result in changes in clinician behaviour, and the over-riding of electronic alerts is common.
- On the whole, reminder systems are beneficial, but these benefits are very context-dependent and there are many examples of no benefit.
- The benefits of reminder systems may fall off quite rapidly when the intervention is withdrawn.
- Examples of reminders improving processes of care are much commoner than those influencing clinical outcomes.
- Reminders can have detrimental effects on workflow such as lengthening consultations.

This ‘review of reviews’ was helpful in planning my research. Whilst the articles provided some key insights, they also reassured me that my major research questions were not already answered. The benefits of reminder systems are generally evident, but their impact is inconsistent and context-dependent. They are not proven in the specific setting of CVD risk assessment and reduction in current UK primary care.

## **1.5 Chronology of the research**

This thesis describes research undertaken over a period of five years 2004-2009. I commenced my current post in March 2004 and registered for the degree in October of that year. At the same time I began working as a part time general practitioner in a practice in Warwickshire. Just prior to moving to the area I co-authored a ‘concept’



paper in the *British Journal of General Practice* (47). During 2004-2005 I undertook much of the preparatory work described in Chapter 5. This involved collaborative work with the private firm Newchurch, at that time contracted to provide an integrated electronic care record resource to the NHS across South Warwickshire. A series of systematic literature searches was undertaken to identify trials of reminder interventions and also papers describing the development of such tools including qualitative evaluations of their use in practice. This was carried out with advice from Warwick Medical School's librarian Diane Clay, and used to support the e-Nudge trial design. A number of the identified papers (48-75) were cited in the trial protocol approved by Warwickshire Local Research Ethics Committee in August 2005 and published in the journal *Trials* in April 2006 (76) (see Appendix).

In early 2006 I collaborated with the company EMIS to develop the e-Nudge software, as it had become evident that the Newchurch platform could not support the trial, and in May 2006 I piloted it in a test practice in Coventry. Reasons for the change from Newchurch to EMIS are discussed in Chapter 5. Minor amendments to the protocol were necessary partly as a result of changes in UK practice, including the introduction of screen reminder messages to support the quality and outcomes framework. These changes are described in detail in Section 8.6 of Chapter 8.

The trial commenced in June 2006 and ran until September 2008. During this time the baseline data following installation of the software were published as a cross-sectional survey (77), and a separate project resulting from the baseline data was undertaken using the QRESEARCH database. This resulted in two further publications (78, 79).

The formal systematic literature review of reminder interventions commenced in September 2007 and was completed in 2009 prior to thesis submission, although it has not yet been submitted for publication. This was a piece of original research separate from the initial literature searches, and resulted in a quantitative meta-analysis described in detail in Chapter 4. Most of the articles identified in the initial searches

were not included in the systematic review as this only included controlled trials operating in the consultation environment. It therefore excluded qualitative and descriptive papers that were nevertheless useful to me in developing the e-Nudge intervention. The formal systematic review was an important part of my training as it gave me the opportunity to develop skills in meta-analysis. Developing these skills was a less urgent priority than commencing the e-Nudge trial as the data that it would generate were required within the 5 year PhD timescale. For this reason, I depended for the design of the trial on the preliminary literature searches that were much broader methodologically.

After the completion of the trial the data collection and analysis took from September 2008 to March 2009. It was submitted to the *British Journal of General Practice* in May 2009, accepted in September 2009 and is due for publication in April 2010 (80).

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## Chapter 2: Cardiovascular risk prediction

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### 2.1 Introduction

This research examines the use of electronic data for the identification and targeting of individuals at risk of cardiovascular disease in primary care. A central focus is the process by which such data are used by practice teams. A related issue is the definition of cardiovascular risk itself. In this chapter I will discuss the usage and definition of cardiovascular disease and cardiovascular risk, the factors used to identify those at risk, and how the coding of electronic information in primary care might influence them. Historically the development of cardiovascular risk algorithms, and in particular the selection of putative risk factors to support them, has been influenced by the availability of objective information, and not only by their relevance to cardiovascular outcomes. This issue has implications for the study of cardiovascular disease in the current primary care environment.

### 2.2 Definitions and usage of ‘cardiovascular disease’ and ‘cardiovascular risk’

The term ‘cardiovascular disease,’ when used in the context of cardiovascular risk, implies coronary artery, cerebrovascular, and peripheral vascular disease. Atherosclerosis, thrombo-embolism, or haemorrhage affecting the *arterial* circulation are the underlying pathological processes or complications. Venous thrombo-embolism is an important cause of vascular mortality and morbidity but its risk factor distribution is sufficiently different from arterial disease that it is considered separately when cardiovascular risk is estimated. The venous circulation is prone to thrombosis, but venous thrombo-embolism is not influenced appreciably by arterial hypertension and much less so by lipid abnormalities than is the arterial circulation. Haemorrhage occurs

in veins but is less often catastrophic and fatal than haemorrhagic events occurring in arteries. Valvular heart disease (congenital or acquired), vasculitic disorders (e.g. temporal arteritis), those involving abnormal vasomotor function (e.g. Raynaud's syndrome, vibration white finger) and congenital abnormalities of the blood vessels (unless causing haemorrhagic stroke) are also excluded from the concept of 'cardiovascular risk' used in primary care.

Atrial fibrillation is an important cause of cardiovascular events that falls outside (or perhaps between) the arterial/venous distinction. The atria are on the venous side of the circulation, but in the case of the left atrium and the pulmonary veins that feed into it, thrombosis may produce emboli directly into the arterial tree. Venous emboli arising anywhere else in the body are prevented from doing so by the need to pass through the pulmonary circulation. Left atrial thrombosis commonly results from atrial fibrillation (AF), in which disorderly contractions produce turbulence and relative stasis, facilitating thrombosis. AF is therefore a very significant risk factor for thromboembolic stroke, but (perhaps because of the difference between the risk factor profiles for arterial and venous disease) is absent from most of the standard CVD risk algorithms, and is considered separately. An exception to this is the recently developed QRISK2 (1), which combines AF with other CVD risk factors within the same algorithm. This is discussed later.

### **2.2.1 ICD-10 Classification**

The definition of CVD is influenced by the particular context in which it is used. e.g. clinical care or research. The World Health Organisation (WHO) developed the International Classification of Diseases (ICD) to standardise definitions for all diagnostic categories. This system originated in the 1850s and was last updated in 1990 as the ICD-10 (<http://www.who.int/classifications/icd/en/>). Relevant diagnostic categories for cardiovascular disease are:

I20-I25	Ischaemic heart diseases
I60-I69	Cerebrovascular diseases
I70-I79	Diseases of the arteries, arterioles and capillaries

These classifications largely involve atheromatous, haemorrhagic, or thromboembolic disorders, but there are exceptions, e.g. cerebral arteritis, hereditary haemorrhagic telangiectasia, and others, which would not have the same implication for vascular prevention in clinical practice.

### **2.2.2 Read codes and SNOMED CT**

More importantly for this research, the Read coding system used in current NHS primary care involves a similar classification to ICD-10 with regard to cardiovascular diseases. Arterial disorders are taxonomically separate from venous disorders even though either may involve thrombosis. For the majority of conditions the Read code groups G3... and G6... refer to disorders involving arterial thromboembolism or haemorrhage. These share a broadly common pathophysiology and range of risk factors, in contrast with venous disorders as discussed above.

SNOMED CT (Systematised Nomenclature of Medicine Clinical Terms), discussed in the previous chapter, was developed in 2002 through a merger of NHS Clinical Terms Version 3 (CTV3) Read codes and the SNOMED RT (Reference Terminology) system in use in the United States. In the process the relationships between different disease states and other medical terms was revised. The four basic elements of SNOMED CT are concepts, hierarchies, relationships, and descriptions. The details are beyond the scope of this thesis, except that the term 'concept' has a specific meaning in SNOMED CT. It is the most basic 'unit of thought' used for specific entities at the lowest taxonomic level (2). The creation of SNOMED CT involved an extensive mapping exercise validated by independent US- based and UK- based data editors. The initial mapping of concepts was followed by a review of the

hierarchical structures defining taxonomic relationships (3). Fortunately for my research the Read codes that are still in use in current general practice provide an adequate taxonomy for cardiovascular disease.

However there are exceptions, in addition to the issue discussed above concerning atrial fibrillation. An important example is the inclusion of ‘Vertebrobasilar Insufficiency’ in the same Read code group as ‘Stroke’. Use of this term, when coded in an electronic record, automatically includes the patient in the Stroke disease register, even though it is not included as such in ICD-10. However, the diagnosis does not necessarily imply cerebrovascular atheroma, or the need to control vascular risk factors. Vertebrobasilar perfusion may typically be impaired by degenerative disease of the cervical spine to which the vertebral artery is intimately related anatomically. Practices have had to rationalise their use of this Read code to avoid this misplacement, if inappropriate to the individual. Similarly, this specific issue had to be accounted for in the measurement of outcomes in the e-Nudge trial described later in this thesis.

### **2.2.3 Research study outcomes**

Research contexts may require alternative definitions to those used in clinical care. Observational or intervention studies require clearly defined outcomes or endpoints. At one extreme, this might be limited to hard outcomes e.g. myocardial infarction, stroke, or coronary death, where it is relatively easy to determine to which category an individual belongs at the end of the study. It would be more difficult to categorise whether a person has a significant aortic aneurysm (a potentially serious arterial complication) unless it ruptured, as aortic aneurysms develop gradually and expand in size over a period of years. Detection on a routine ultrasound scan or during a clinical examination could not easily be included as an outcome event in such a study, unless the entire study population were screened and a minimum diameter defined as a diagnostic threshold. For larger studies, this is not a practical option. Study design therefore also determines the usage and concept of cardiovascular risk.

This issue also applies to some of the commoner cardiovascular outcomes, including angina pectoris, transient ischaemic attack (TIA), and heart failure. Until the mid- or late-1990s, the diagnosis of angina was largely a clinical one, based on history taking. Since then, most patients with suggestive symptoms have been referred for investigations to confirm the diagnosis prior to their entry on Coronary Heart Disease registers. A diagnosis of angina has become a much more objective outcome. Transient ischaemic attacks are largely a clinical diagnosis, as by definition the neurological deficit resolves within 24 hours of onset (without associated infarction detectable on brain imaging), but they are now usually followed up by investigation. 'Fast-track' neurovascular clinics are now widespread and have streamlined referral pathways, improving the quality of this diagnosis as an indication of significant cerebrovascular disease over the past ten years. This in turn has improved the quality of the general practice registers, to which a patient will be added when the diagnosis is confirmed. In practice this simply requires the entry of the relevant Read code into the record with the date of onset, as discussed in the previous chapter. Feigin and Hoorn recommend the inclusion of general practice registers for case ascertainment in stroke/TIA incidence surveys (4), based on the success of this technique in the OXVASC study (5). However, in general practices not participating in research studies the diagnosis might be less reliable. Heart failure is a further example. The Quality and Outcomes Framework (QOF) of the new General Medical Services contract now requires this diagnosis to be confirmed by echocardiography, improving considerably the quality of practice based heart failure registers.

These clinical diagnoses are now much more likely to be supported by investigations. The question then arises over how the modern diagnosis compares with the outcome definition used in classical research studies such as the Framingham Heart Study. The Framingham investigators studied cohorts that were followed up intensively, but used outcome assessments that only required questionnaires, physical examination, office measurements, electrocardiographs (ECGs), and death certificates

(6). All the patients they diagnosed with coronary artery disease had symptomatic angina, a history of myocardial infarction, or evidence of silent myocardial infarction on ECG. Even for 'hard' events, technology may affect detection rates significantly. For instance, the OXVASC investigators commented on the effect of introducing sensitive biomarkers including troponins on the rates of diagnosis of myocardial infarction (7). The ICD classification discussed above was used as a basis for diagnostic definitions of CVD events in the OXVASC study, even though the primary source of their data (general practice records) utilises the Read code classification system. As discussed above, both of these systems (ICD and Read coding) make a distinction between arterial and venous events, and between coronary, cerebral, and peripheral arterial events.

The Framingham Heart Study is still the most frequently used data source for the identification of cardiovascular risk. It used a number of different outcomes and has alternative algorithms (using different co-efficient values) for the following (8):

- Myocardial infarction (MI) including silent and unrecognised MI
- Coronary Heart Disease (CHD) death (sudden or non-sudden)
- CHD (including MI, CHD death, angina pectoris and coronary insufficiency)
- Stroke (including transient ischaemia)
- Cardiovascular disease (all of the above plus peripheral vascular disease and heart failure)
- Cardiovascular death

Here, 'cardiovascular disease' includes all of CHD, stroke, transient ischaemic attacks (TIA), peripheral vascular disease and heart failure. These outcomes are included in the Framingham CVD algorithm. However, the Joint British Societies (9), also using the Framingham data, have a different definition of 'cardiovascular disease'



that is a simple summation of the risks calculated from the CHD and Stroke/TIA algorithms (i.e. not including peripheral vascular disease or heart failure). The same approach is used in the subsequent QRISK algorithm described later (1, 10). The justification for this is firstly that peripheral vascular disease (PVD) is much more difficult to define, for the reasons discussed above. Many older patients have a degree of it, often without obvious symptoms. Most patients reporting symptoms will have the diagnosis made only on clinical grounds (not confirmed through investigations), and practices are not currently required to have PVD registers, so diagnosis and recording (particularly electronic) is less consistent. Secondly, heart failure is not always due to coronary artery disease, but may be found in patients with cardiomyopathies, valvular disorders (congenital and acquired), as a complication of hypertension, or associated with other pathogenic mechanisms. It does not necessarily imply ischaemic vascular disease associated with atheroma.

#### **2.2.4 Sudden death from cardiovascular disease**

Unless due to trauma, sudden death is usually caused by a vascular event. An exception to the above distinction between venous and arterial disorders therefore arises when an individual dies suddenly from pulmonary embolism. In this case, the event would only be included as a relevant outcome if death was 'sudden'. This in itself requires a definition. In the MONICA study discussed below, death within 24 hours of hospital admission was suspected to be vascular and required monitoring (11). Later in this thesis the issue of sudden cardiovascular death is discussed again as it represents a 'vulnerable' area of data quality in primary care (Chapters 6 and 7).

## **2.3 Risk factors and their independence**

As well as the outcome measures, the selection of risk factors as inputs to the algorithms may be biased towards those that are independent, objective and easily measurable. For instance, in the Framingham Heart Study:

*“The components of the profile were selected because they are objective and strongly and independently related to CHD and because they can be measured through simple office procedures and laboratory results.” (12)*

### **2.3.1 Framingham risk factors**

The risk factors used in the Framingham algorithm were:

Age

Gender

Smoking status

Blood pressure (usually based on systolic)

Total serum cholesterol

Serum high density lipoprotein (HDL) cholesterol

Diabetes status

Presence or absence of Left Ventricular Hypertrophy on ECG

Other factors were measured, but these are the ‘classical’ factors that have become the inputs for the most commonly used algorithms derived from this study’s data.

### **2.3.2 Definitions used by Framingham investigators and issues arising**

Age and gender were uncontroversial. Smoking status was considered positive in any participant reporting tobacco use in the past 12 months, i.e. those quitting for a longer

interval become non-smokers. (More recently, the CHD National Service Framework (13) and JBS2 (9) recommend that smoking status should be based on lifetime exposure, and that an ex-smoker should be considered a 'current smoker' until 5 years have passed since quitting for the purposes of a Framingham risk estimation. However the original definition was based on 12 months). Systolic blood pressure was based on the average of two office readings taken on the same day. Cholesterol levels were measured using laboratory techniques that are equivalent to modern practices. Diabetes status was based either on use of hypo-glycaemic drugs or insulin, or a single raised blood glucose measurement. In the recruitment of 1968-1975 this level was 150mg/dl (8.3mmol/L approx) on a casual (random) measurement. In the later 'Framingham Offspring Cohort' recruitment phase, the definition was altered to include all those with a fasting plasma glucose level of  $\geq 140$ mg/dl (or  $\geq 7.8$ mmol/L). The modern diagnostic threshold based on a fasting plasma glucose is now  $\geq 7.0$  mmol/L following revision to the World Health Organisation criteria in 1999 (14). (Discussions are currently underway likely to revise the diagnostic definition for diabetes to one based on glycosylated haemoglobin rather than blood glucose values, a technique developed during the 1980s and therefore unavailable to the original Framingham investigators.) This change has significantly altered the proportion of the population considered to have diabetes and contributes to the rise in recorded prevalence over the past ten years. The Framingham investigators treated diabetes status as a binary input (diabetes present or absent). In recent years, people with diagnosed diabetes have not been risk assessed using the Framingham algorithm, and have been considered to be generally at raised risk. However there is increasing recognition of the *continuous* rather than binary nature of hyperglycaemia as a CVD risk factor and this is reflected in the UKPDS risk algorithm which takes account of both the level of glycosylated haemoglobin and duration of diabetes in the individual (15). For those without diagnosed diabetes there is a grey area of impaired glucose regulation below the diagnostic threshold for diabetes, particularly in association with central obesity and

other risk factors as the ‘metabolic syndrome’ (16). The Joint British Societies suggest that patients with impaired glucose tolerance (but not diabetes) are at about 1.5 times the risk estimated using the standard Framingham equation (9). There is some evidence that recognising the metabolic syndrome in clinical practice improves the assessment of cardiovascular risk (17). However, its value for clinical care continues to be debated (18, 19).

Whilst other risk factors were recorded during the Framingham Heart Study, the Framingham algorithms include the factors believed to be *independently* related to the development of cardiovascular disease. Other variables may influence risk through the ‘classical’ factors. For instance, body mass index (BMI) is related to diet and exercise, both of which are reflected to some extent in the serum cholesterol profile and through the blood pressure input. Adding BMI to the Framingham algorithm does not significantly improve its predictive performance (12). Diastolic blood pressure is similarly omitted because it is so strongly correlated with systolic blood pressure that to include both would create statistical redundancy, making interpretation more difficult (12). A separate algorithm is available using diastolic instead of systolic blood pressure, with slightly different co-efficient values, but is rarely used in practice. Family history exerts its effects partly through the lipid profile and blood pressure inputs, which include heritable components. So whilst family history is extremely significant as a risk factor, much (but importantly not all) of its influence is conveyed through the cholesterol profile and blood pressure level. The independent relevance of family history is recognised by the Joint British Societies, who recommend that it be taken into account in assessing the risk of an individual, and more recently by NICE CG67: Lipid modification (20). Family history partly ‘covers’ some of the risk attributable to ethnicity (21).

### 2.3.3 More recent approaches

Since the original Framingham study, new factors have been identified, but in most cases their influence is already at least partially represented. This explains the ‘diminishing returns’ phenomenon (21) through which the addition of further variables beyond the classical factors adds less and less to the algorithm’s performance as a predictive tool. This preference for minimalism in the algorithm restates the desire of the original Framingham investigators (as quoted above) for strong, independent factors. The Framingham Heart Study led on to intervention studies that demonstrated the impact of risk factor control on cardiovascular events, particularly blood pressure reduction (22) and lipid lowering (23). Only by modifying *causative* factors will risk be reduced and outcomes improved. However, current policies on lipid lowering and blood pressure reduction advise the targeting of individuals based on overall risk, and not simply on lipid or blood pressure values respectively. Modification of causative factors is most effective in those whose overall risk is highest. This is the basis for the current policy on statin therapy, which recommends treatment in all people at high risk of CVD irrespective of pre-treatment values (20). More recently, the case has been made for blood pressure reduction in those at risk of CVD even when the pre-treatment level is normal (24, 25). Jackson et al made this case particularly clearly in a review paper in which they highlighted the interactive nature of risk factors and the rationale for basing treatment decisions on absolute risk and not on individual risk factor levels (26). However, current policy on treating blood pressure still requires the pre-treatment level to be at least elevated to 140-159mmHg systolic or 90-99mmHg diastolic for the general population, combined with raised CVD risk.

The need to identify those at highest overall CVD risk sets an important task for primary care and has become the focus of this thesis. Improvements to the ‘classical’ risk algorithms (most of which are derived from the Framingham Heart Study data) might take advantage of risk variables that have become available since this study took place, including currently available electronic data. An example of this is the inclusion

of deprivation scores in the ASSIGN algorithm published in 2007 (21). Deprivation affects cardiovascular risk in a number of ways, some of which are conveyed through the ‘classical’ risk factors. Unemployment, for instance, is known to be associated with adverse values of the classical risk factors (27). But when classical algorithms are used to predict cardiovascular outcomes in areas of high deprivation, they tend to underestimate risk (21). This contrasts with their tendency to over-predict among the general population (28). This suggests that the association of deprivation with cardiovascular risk is not simply due to the confounding effects of the classical factors. It suggests either that other factors associated with deprivation are independently involved or that the algorithm that weights and combines the known risk factors needs to be adjusted for use in these populations. This has implications for the targeting of interventions, as it means that reduction of blood pressure and cholesterol may be more worthwhile in a deprived inner city environment than in a more affluent situation, all other things being equal.

## **2.4 Absolute and relative risk**

The current approach towards risk factor management for CVD prevention is based on the principle that control of risk factors is most justifiable in those at highest short or medium term (10 year) absolute risk. Such patients have a need for drug therapies whose safety and effectiveness have been demonstrated over timescales of years rather than decades. However, this approach may neglect younger patients whose estimated absolute risk will generally be low (because age is such an important factor) but whose relative risk compared to age matched peers may be high, and whose life time risk is high. Such people are likely to benefit in the longer term from risk factor control in terms of added life years. Recognising this problem, the Joint British Societies in their first report of 1998 recommended basing treatment on the individual’s projected risk to age 60 years (29). In the subsequent second report, this strategy was replaced through

the development of a new algorithm introducing a more complicated age adjusting factor (9). In this approach, patients who are less than 50 years are all assumed to be 49 for the purposes of calculating risk (which is only recommended in people under 40 years in special circumstances). Those between 50 and 59 years are assumed to be 59, and those who are 60 years and over are all assumed to be 69. This approach therefore leads to an over-estimation of risk in people who are less than 49, between 50 and 58, and between 60 and 68, with an under-estimation in people over 70 years. This manoeuvre is designed to offset the tendency of the Framingham algorithm to focus attention excessively on the elderly population in primary prevention.

## **2.5 Missing data**

Whether in a clinical or in a research context, the issue of missing data commonly arises. For Framingham risk estimates, profiles not uncommonly have either the HDL cholesterol level missing, or the LVH status unknown. A number of risk assessment tools have been designed to take account of these potential data inadequacies (e.g. (30)). Very commonly, assumed values are imputed where data are missing. This approach may fail to recognise that missing data are not necessarily distributed in the same way as recorded data, a problem discussed by Sterne et al as applied to research and epidemiological contexts (31). This is not just an issue for current primary care, but was also a problem for the Framingham investigators. In the equations developed prior to the 1968-1975 cohort, HDL cholesterol was not included. From 1968 onwards it was recorded, as the improved predictions resulting from its inclusion had become evident (12). In some individuals, information on either LVH or diabetes status was unavailable, and if so was assumed to be negative. Modern approaches using the Framingham algorithms also need to account for missing data. This issue will be discussed in detail later in this thesis.

## **2.6 Pre-treatment and modified risk factor values**

For the years that followed the 1968-1975 Framingham cohort recruitment, at least until the 1980s, effective treatment of risk factors using drug therapies was relatively uncommon, although antihypertensive drugs were used increasingly in subsequent years. Lipid lowering therapy did not become commonplace until the 1990s. A reduction in smoking occurred in men (although not in most female populations, where it tended to rise), and blood pressure and cholesterol values tended to decline, contributing to the global improvement in coronary heart disease mortality since the 1980s (32).

The Framingham study therefore took place in an environment relatively free of the effects of risk factor modification on outcomes. This raises a further issue, as the estimation of cardiovascular risk using the Framingham algorithms is required for modern populations whose future risk may be affected by drug therapy, and whose risk estimation should theoretically be carried out using 'pre-treatment' values of blood pressure and cholesterol. In modern practice, such values are often unavailable if the patient is already on treatment, particularly when the drug therapy preceded the introduction of electronic medical records. In the UK, this began in the late 1980s or early 1990s. By the end of the latter decade the majority of UK practices were computerised to varying degrees. Nevertheless, as discussed above a significant proportion of modern patients have treated risk factors whose pre-treatment values are either not recorded or recorded in a form not accessible to electronic retrieval.

Lack of availability of 'pre-treatment' values for blood pressure and cholesterol creates a practical difficulty, and an obstacle to the estimation of risk in treated individuals. Such individuals include the majority of those on the hypertension register, which was recommended in the Coronary Heart Disease National Service Framework (13) as the most likely place to begin case finding for those at high coronary heart disease risk. A systematic attempt to identify the practice's 'at risk' population will



therefore miss these patients if it is confined to those who are not currently taking anti-hypertensive or lipid lowering drug therapy, although this approach has been advocated (33). A similar approach was recommended by JBS2, in which patients off treatment were to be risk assessed opportunistically.

Other solutions have included:

- Recognising the problem but still using the modified values as inputs, accepting that cardiovascular risk will be under-estimated. This is the approach used in the 'e-Nudge' case-finding tool to be described in detail later in this dissertation. It is also suggested in the 2008 NICE guidance on Lipid Modification (20).

- Using 'treatment for blood pressure' status as an input to the algorithm. This is used in the Pocock algorithm (34) and in the later QRISK and QRISK2 algorithms (1, 10).

- Introducing an interaction term between systolic blood pressure and anti-hypertensive treatment (35).

- Entering an 'assumed value' for the pre-treatment levels of blood pressure or cholesterol. JBS2 (9) suggests a systolic blood pressure of 160 mmol/L and a total to HDL cholesterol ratio of 6.0 as the assumed values.

- In a new Framingham based risk algorithm designed for use in primary care, D'Agostino et al provide alternative regression co-efficients for systolic blood pressure depending on whether it is a treated value or not (36).

The Framingham study has become the most frequently used data source for estimating cardiovascular risk, partly because of the relative freedom from the effects of treatment on outcomes. Because of the global improvement in cardiovascular mortality since the original study was completed, the CHD algorithm has been found to over-predict risk in the general population of the UK (28), in Germany (37), and in

Belfast and France (38). In the UK, over-estimation is particularly evident in the low risk populations as discussed above (21).

The Framingham algorithms themselves have experienced numerous revisions over the years. An early risk scoring system was published in 1967 (39) and drew on the data collected from the original recruitment cohorts that commenced in 1948. A widely cited paper from 1976 (6) describes a new logistic regression algorithm to combine the risk factors but at this point high density lipoprotein (HDL) cholesterol was not included. The algorithm in current common use is that published in 1991 (8) and includes HDL cholesterol. This was further modified in 2000 to enable it to predict cardiovascular events in patients with established cardiovascular disease such as a history of myocardial infarction, i.e. in the secondary prevention scenario (35) although this algorithm has not entered routine practice in the UK.

The contrast between ‘pre-treatment’ and ‘modified’ risk is particularly relevant if one is attempting to create practice based ‘At risk of CVD’ registers. This was first proposed by the CHD NSF of 2000 (although this document was concerned more specifically with CHD rather than CVD risk). Such registers would include people whose risk had been identified on the basis of pre-treatment risk factor measurements (e.g. blood pressure and serum cholesterol) but who had subsequently undergone treatment of these factors to the point where the estimated risk based on treated values would be lower than that required to justify inclusion on the register. This raises the important issue for identifying potentially at risk individuals based on current electronic data: are we interested in identifying those that are still at risk when assessed using treated factors values, or are we interested in controlling risk in those whose ‘original’ (unmodified) risk was high? The CHD NSF of 2000 clearly preferred the latter, whilst more recent guidelines (such as NICE CG67) that recognise the difficulties (increasingly evident since 2000) in identifying pre-treatment levels in general practice tend to favour the former, with appropriate adjustment in risk estimation to account for this difference.

## **2.7 Cardiovascular risk algorithms using alternative data to Framingham**

Other important studies contributing to what is known about cardiovascular risk include MONICA (40), PROCAM (41), SCORE (42) ASSIGN (21) and QRISK (1, 10).

### **2.7.1 MONICA**

MONICA (Monitoring trends and determinants in cardiovascular disease) was a large prospective observational survey of cardiovascular risk factor patterns and event rates organised by the World Health Organisation, involving 41 collaborating centres in 21 countries, and a total study population of approximately 15 million people aged 25-64 years. It was designed to investigate the relationships between trends in CVD risk factors and CVD mortality rates (43). The original Framingham study included 5573 individuals, a small enough number to allow an intensive follow up strategy. MONICA involved much larger numbers and required alternative approaches. Designed prospectively and conducted using protocols standardised across collaborating centres, MONICA is an early example of epidemiological surveillance of cardiovascular disease patterns using routinely collected health data on an international scale. This source created quality issues in event monitoring (11). Differences in ascertainment occurred between collaborating centres. Some used the 'hot pursuit' method, in which patients admitted to hospital following an event would be interviewed whilst still an inpatient. Others used the 'cold pursuit' approach, in which event monitoring relied on searches on hospital records following discharge (44). Hense et al suggested that blood pressure measurement quality in MONICA should be assessed not simply by visits and inspections of the collaborating sites, but by examining the actual blood pressure measurements themselves (45). Two techniques, the 'last digit preference' and the

'proportion of identical duplicate measurements' were shown to improve the comparability of quality standards between centres. In the two Belgian collaborating centres, misclassification of CHD cases was found to be partly due to coding problems (46). This issue is likely to affect any research relying on diagnostic coding, and will be discussed further later in this dissertation.

MONICA was designed primarily as a longitudinal survey of diverse multinational populations rather than a cohort study with individual follow up (although this did also occur). It did not therefore result in a risk algorithm, other than through its contribution to the SCORE project, which included MONICA cohort data from Scotland and Germany (42).

### **2.7.2 PROCAM**

PROCAM (Prospective Cardiovascular Munster study) was a cohort study based at Munster in Germany, commencing in 1986 (41). The study confirmed the relevance of the classical risk factors, and suggested that serum triglycerides, apolipoprotein b, and coagulation factors were also relevant to CHD risk and might be used to improve risk estimations. The main outcomes in this study were myocardial infarction and sudden cardiac death. Cerebrovascular disease outcomes were recorded, but the upper limit of the age range was 65 years, above which stroke incidence rises steeply (7). Interestingly, this study raised the question of a 'J-shaped curve' relating total and LDL cholesterol levels to all cause mortality, due to an apparent increase in cancer deaths in smokers with low levels of these factors (47).

### **2.7.3 SCORE**

The SCORE (Systematic Coronary Risk Evaluation) algorithm is based on examination of 12 different cohort studies from 11 European countries (42). The outcomes only include fatal cardiovascular events. Whilst these data are from European rather than North American populations, the SCORE algorithm was not considered superior to

Framingham for the UK population in the JBS2 report or in the 2006 NICE guidelines on statin prescribing (48). One of the reasons for this was the need to include non-fatal as well as fatal CVD outcomes.

SCORE does not include diabetes status as an input risk variable, recognising that patients with diabetes should generally be considered at high CVD risk. This became the recommended approach supported by the British Hypertension Society (49), the Diabetes National Service Framework (50, 51) and JBS2 (9). However, risk algorithms have been derived for patients with diabetes from the United Kingdom Prospective Diabetes Study for both CHD (15) and stroke (52). The CHD algorithm has been compared with the Framingham CHD function in a study of patients with newly diagnosed type 2 diabetes but free of CHD (53). Both algorithms were found to be poorly calibrated to the study population's outcomes, although discrimination was moderately effective. However the most recent NICE guideline on type 2 diabetes recognises that not all patients are at sufficient cardiovascular risk to justify lipid lowering therapy and that in such cases a risk assessment should be undertaken on an annual basis using the UKPDS risk engine (15).

#### **2.7.4 QRISK and QRISK2**

More recently, a new risk algorithm based on UK data was derived using the QRESEARCH database at the University of Nottingham (54). This algorithm was named QRISK (10) and was later improved to produce QRISK2 (1). Based exclusively on data held in EMIS practices, the algorithm was later validated using the THIN database (which involve VISION (In Practice Systems) data) and found to out-perform Framingham as a predictive tool for CVD events in the UK population (55). However, as discussed above (and very clearly stated by Liew and Glasziou (56)), it may be more appropriate to address the concept of underlying, untreated risk rather than the risk based upon outcomes of populations whose CVD risk factors are being actively managed.

### **2.7.5 Comparisons between Framingham and alternatives**

The Framingham risk function has been compared with European algorithms including Dundee, British Regional Heart Study (BRHS), and PROCAM (57). The algorithms were applied to a sample of 206 consecutive male patients attending a hypertension clinic. Apart from the BRHS data (in which systematically lower risk estimates were produced), Framingham made comparable predictions to the other algorithms and was considered adequate for use in Northern European male populations.

Framingham algorithms have also been applied to different ethnic groups to test external validity, as the Framingham study population was predominantly composed of white Americans. The multiple ethnic groups investigation (58) examined data from six prospective cohort studies in ethnically diverse populations. The algorithm performed well among white and black men and women, but required recalibration for Japanese American and Hispanic men, and Native American women.

The validity of the Framingham algorithm in the modern UK population remains a concern, particularly in Asian men, whose observed risk tends to be higher than the predicted risk using Framingham. To estimate the diverse risk levels of different minority groups, the ETHRISK algorithm was developed, based on survey data from UK populations (59). However, this has not yet been validated through a cohort study within these populations.

## **2.8 Alternative models for risk prediction**

This section describes the background and justification behind the development of past and current statistical models for CVD risk estimation, and the options for future models based on primary care data. I will describe the basic structure of the logistic regression model originally used by the Framingham investigators, explain how this model was later developed, and end with a discussion over the advantages and

disadvantages of newer approaches. The purpose of this is to consider whether more complex models offer advantages over existing options, as this was an original research question motivating the thesis (60).

### 2.8.1 Basis for original and subsequent Framingham CVD risk equations

Logistic regression is typically used for classification or regression problems involving multiple categorical, binary or continuous predictor variables and a *binary* outcome (dependent variable) such as development of a disease. This is the model used for the original Framingham risk function presented in 1976 by Kannel, McGee and Gordon (6). In such cases, the outcome (e.g. development of CVD) is not continuous and Normally distributed, a requirement of linear regression analysis.

In logistic regression, a logarithmic transformation of the odds ratio (the 'logit') is used instead of the probability of a positive outcome. This avoids deriving meaningless probability values greater than 1.0 or less than zero (61). The other advantage of the transform is that the logit takes values from  $-\infty$  to  $+\infty$ , allowing confidence intervals to be derived around an estimated value within this range. The logistic regression equation can then take a form similar to a multiple linear regression function, with the dependent variable (the logit) equal to the sum of an intercept (constant) and a number of predictor variables, each multiplied by its regression coefficient:

$$\text{Log (odds ratio)} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 \dots \dots \dots \quad [\text{Equation 1}]$$

where  $\beta_0$  is a constant and  $\beta_1, \beta_2, \beta_3, \dots$  are the regression co-efficients for each risk factor  $X_1, X_2, X_3, \dots$  etc.

Fitting the equation to the data involves maximum likelihood techniques to derive the optimal intercept and co-efficient values.

The relationship between risk factor values and the outcome is non-linear, but the log (odds ratio) is a linear function of the co-efficient values (Equation 1). Each risk factor ( $X_1$ ,  $X_2$ ,  $X_3$  etc) makes an independent contribution to the outcome. The proportion of overall risk attributable to each risk factor is estimable. The logit can be transformed back to produce a probability value  $p$  for a positive outcome:

$$p = 1 / (1 + \exp(-(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 \dots))) \quad [\text{Equation 2}]$$

In survival analysis (where the outcome of interest is the time to death or development of some other end point) the *Cox proportional hazards* model is appropriate. This uses the *hazard ratio* (HR) in place of the odds ratio. The HR is the ratio of the hazard of developing the disease in the presence of one or more risk factors to the hazard in a comparator population with zero or baseline risk factor values (61). The outcome of the risk function is the log of the hazard ratio (rather than the log of the odds ratio).

Whilst Cox regression introduces a continuous dimension (the timescale at which the hazard ratio may be measured), the hazard still relates to binary outcome events. The Cox model includes an assumption that the hazard ratio itself is constant over time, even though the hazard itself may be rising or falling with time. An individual who is twice as likely to develop the disease as another individual after (say) five years remains twice as likely after ten years, even though the hazard for both may have increased. The probability distribution of the baseline survival function does not need to be specified if the constant hazard ratio assumption is valid. Cox proportional hazards was brought in to Framingham risk modelling subsequent to the original logistic regression model, to recognise the importance of the time dimension in CVD risk, and is used by Anderson et al in paper published in *Circulation* in 1991 (12).

A subsequent paper led by Anderson in the same year (8) introduced an assumption that the time  $T$  to an event follows a Weibull distribution. This distribution



is appropriate for degenerative processes (both in medicine and engineering) where functioning components of a system tend to ‘wear out’ over time. For those at risk of a cardiovascular event, the hazard increases over time (although the hazard ratio may still in principle remain constant). Anderson et al in this later paper claimed superiority of the new algorithm over both the logistic regression and Cox proportional hazards precursors, and this model became the basis for the most widely used Framingham algorithm. The co-efficients from this paper were used in the programming of the e-Nudge algorithm described later in this thesis.

In the regression models described so far, interactions between risk factors are assumed to have a relatively minor influence on outcomes, but can be built in if expected to be important. For instance, in the Anderson equation (8), interactions between age and female gender, and between left ventricular hypertrophy and male gender, were built in to improve the statistical fit. These authors also introduced a quadratic term, the  $(\log(\text{age}))^2$ , as an additional risk variable, and also built in an interaction between this and female gender. These were found to improve the performance of the standard equations.

This discussion is intended simply to illustrate that traditional CVD risk equations, whether based on logistic regression, Cox proportional hazards, or a Weibull model, are designed to identify the independent influence of the explanatory variables and include a limited range of interaction terms. The interaction terms (and the quadratic term mentioned above used by Anderson et al) have the same status as the other weighted risk variables in the function linking predictors to outcomes (e.g. Equation 1 for logistic regression). This approach is designed to identify the most important risk factors and to measure their relative contributions to overall risk.

## 2.8.2 Structure of more recent risk algorithms

During the 1990s and 2000s other risk algorithms were developed, as discussed above. The most important of these were PROCAM, SCORE, ASSIGN, QRISK, and D'Agostino 2008.

PROCAM (41) used a standard Cox proportional hazard model as the basic multivariate risk algorithm.

The SCORE (42) project, involving the synthesis of data from cohort studies in 12 European countries, used the Weibull proportional hazards model as discussed above. A separate hazard function was derived for men and for women in each contributing study, and the results were collated to produce an overall risk function. An assumption was made that risk factors have similar effects in both men and women and across different countries. The authors compared the performance of the Weibull model with a Cox proportional hazards model to test the validity of their estimate of the baseline survival curve.

The ASSIGN project (21) used a Cox proportional hazards model. This was the first algorithm to demonstrate improvement in CVD risk estimation through the inclusion of family history and social deprivation (measured by the Scottish Index of Multiple Deprivation, SIMD). A different function was developed for men and women as it was evident that in women (but not men) a significant interaction was present between sex and deprivation. Risk factors were only included in the final model if they were significantly and independently related to cardiovascular outcomes in both sexes.

The QRISK and QRISK2 projects (1, 10) also utilised Cox proportional hazards models and again derived co-efficients for men and women separately. QRISK included, in addition to the 'classical' Framingham risk factors: deprivation linked to Townsend scores (based on Postcode output areas of about 125 households); body mass index; existing treatment for hypertension; and family history of premature coronary heart disease. The QRISK2 algorithm also added self-assigned ethnicity, type2 diabetes, renal disease, atrial fibrillation and rheumatoid arthritis to this list. In the

QRISK projects, interactions between various factors were tested and quadratic terms inserted (as described above for Anderson Framingham).

In 2008, D'Agostino et al produced a new algorithm specifically tailored to the primary care environment and based on Framingham data. It used data from the later offspring cohort (unavailable to the original investigators of the 1968-1975 algorithm), and therefore included more CVD events. It included (as mentioned above) a means of taking account of blood pressure treatment. This algorithm also used Cox proportional hazards as the basic regression model.

### **2.8.3 Other possible risk models**

The algorithms described so far have certain characteristics in common. The underlying model structure and risk factors were generally selected *a priori* and the studies are termed *prospective*, although the cohort populations used for QRISK and QRISK2 were identified retrospectively. Potential interactions between risk factors have been built in and tested to varying extents.

An alternative approach involves more complex data mining models including artificial neural networks (ANNs). The following section will give some background to this general approach and then discuss examples applied to the area of CVD risk.

### **2.8.4 Background to artificial neural networks**

ANNs have become widely used in engineering and industry, where there is frequently a need to recognise patterns in datasets for classification or outcome prediction. The superiority of this over traditional approaches is greatest when a large number of interactive factors are present. The potential for introducing neural networks into medical care was discussed in a series of articles dedicated to this topic in the *Lancet* during late 1995 (62-71). More recent articles have continued to make this area conceptually accessible to clinicians and the range of applications within medicine has increased. A PubMed search that I conducted on 16.8.09 for review articles on *Neural*

*networks* (MeSH) limited to core clinical journals with no date range returned 28 citations. I found the most informative of these, in addition to the Lancet series, to be a paper by Ohno-Machado and Rowlands (72) and one by Drew and Monson (73).

Ohno-Machado and Rowlands describe the basic structure of ANNs and compare them with simpler models such as logistic regression. Describing their structure in detail is beyond the scope of this thesis, but the following characteristics distinguish ANN models from less complex approaches:

- The influence of individual input risk variables on outcomes may be very context dependent (i.e. dependent of the values and patterns of other factors), and may be less clearly significant in isolation (i.e. independently, as discussed above).
- Interactions between inputs are much more important in determining outcomes than in traditional regression models.
- ‘Training’ of the network (i.e. optimisation of the internal weight values) occurs automatically through exposure of the model to the dataset. The weights are usually set with random initial values and these are then adjusted iteratively through a process of ‘learning’ in which the input data and the actual outcome for each subject (e.g. patient) in the training dataset is presented to the network. The most frequently used training technique is based on the principle of ‘back propagation’, in which the error detected between observed and expected outcomes automatically adjusts the weight values until the error is minimised.
- This machine learning occurs with minimal supervision by the human investigator. The ANN ‘discovers’ its own interaction patterns without preconceived assumptions being built in *a priori*.

### **2.8.5 Published uses of ANNs for future CVD prediction**

The ANN approach has been used to address the issue of cardiovascular risk in at least two separate scenarios: the first using a dataset from a small study of lipid fractions by

Lapuerta et al (74); the second utilising a large dataset from the PROCAM study (75). In the latter study Voss et al compared the standard logistic regression (LR) approach with two types of ANN in their ability to identify high risk groups for coronary events in the PROCAM dataset. One of the ANNs, a multi-layer perceptron, outperformed the LR model, producing a significantly higher area under the receiver operating characteristic curve (AUROC). The LR identified 8.4% of the men as 'high risk,' of which 36.7% suffered a coronary event over 10 years. The multi-layer perceptron identified 7.9% of the men as high risk, and 64% suffered an event. In a commentary on this article Margaret May drew attention to the considerable potential for this approach to improve identification of the highest risk groups. However, she also emphasised the need to ensure generalisability of the model to alternative data sources (76).

Despite this apparent success, complex modelling of cardiovascular risk has not so far seriously challenged more traditional approaches in clinical settings. Reasons for this may include:

1. As above, a preference for minimalism that inevitably places the emphasis on independent factors and downplays the interactions between them, as already discussed.
2. The 'black box' anxiety (71): models derived from neural networks may function well in terms of predictive performance but we may not understand in detail what is actually happening computationally inside the algorithm.
3. A preference among most statisticians for *frequentist* rather than *Bayesian* analysis (77).

Any attempt to utilise more complex models will need to address these issues and demonstrate superiority over traditional approaches in terms of consistent predictive performance when tested in new environments.

### 2.8.6 Advantages and disadvantages of ANNs

A summary of the potential role of the ANN approach is given by Drew and Morton (73):

*"In general, a neural network may be superior to a standard statistical analysis in nonlinear relationships when the importance of a given prognostic variable is expressed as a complex unknown function of the value of the variable, when the prognostic impact of a variable is influenced by other prognostic variables, or when the prognostic impact of a variable varies over time."*

The advantages and disadvantages of ANNs and other complex models may be compared with those of more standard approaches.

In standard approaches, the problems include the models' inability to identify useful interactions between inputs without the foresight of an investigator, who needs to actively build such interactions into the model and then test their influence. The range of possible interactions is inevitably limited and may be biased by preconceived expectations. Opportunities may be lost to include useful non-independent factors due to concerns over statistical redundancy. In addition, the logistic regression algorithm structure cannot easily accommodate 'linearly inseparable' classes. These include 'J-shaped curves,' where the outcome does not change continuously with the predictor, but instead experiences a reversal of direction. In the setting of CVD risk, this is known to occur both with alcohol consumption (78) and with body mass index (79). In the PROCAM study, another example mentioned above was suggested between mortality and serum total and LDL cholesterol, although the excess risk at low levels was found to be due to an excess of lung cancer deaths in smokers with low cholesterol levels (47). As lung cancer mortality is a different outcome to CVD mortality, it could be argued that this example is invalid. Nevertheless, complex risk factor profiles including

J-shaped relationships might well require more complex pattern recognition techniques than those of standard regression models.

Finally, the neural network model has the theoretical advantage that it can recognise correlations between risk factor inputs more flexibly than conventional regression models and so potentially offers greater robustness to missing data. This problem is a significant issue in the development of modern CVD risk algorithms derived from primary care data, including QRISK and QRISK2.

For ANNs, in addition to the anxieties listed 1-3 above, problems include:

1. **Over-fitting.** Any dataset containing predictor variable and outcome values inevitably includes a component of random variation that is not attributable to the predictor-outcome relationship, and should be ignored when fitting a model to the data. The fitting of a traditional (e.g. logistic) regression algorithm involves identifying the function that minimises these residuals, as discussed above. But neural networks are sufficiently flexible to fit the function to the random noise also. If measures are not taken to prevent this, the ANN will perform less than optimally when applied to a new dataset.

2. **Getting stuck on local maxima.** The training of a neural network involves an exploration of a large space of possible internal weight values in search of the optimum weight set. For large datasets, an exhaustive exploration of all possibilities is in practice an intractable problem. The network attempts to reduce the dimension of the classification task, but there remains a risk that a set of weight values will be discovered that is adequate but inferior to the optimum weight set in terms of predictive performance. Rather like a rambler attempting to find a high spot on a landscape, there is a risk of getting stuck on a foothill and never reaching the summit if the strategy is always to follow the upward gradient locally.

## 2.9 Summary

The definition of cardiovascular risk has a long history that spans the introduction of electronic coding into routine health care. The availability of relevant information has been important throughout this time both in conceptualising and actually estimating cardiovascular risk. These issues affect both risk factors and outcomes, and must be accounted for in any initiative aiming to systematically reduce cardiovascular disease in the population. This is particularly the case in primary care, where recorded data may be less ‘tidy’ (in terms of quality and completeness) than those generated by a prospectively designed research study.

Since the original development of CVD risk algorithms based on the Framingham Heart Study, new approaches have been developed to improve the targeting of the ‘at risk’ population for effective interventions. These approaches have also been guided to some extent by the availability of relevant data. More recent cohort studies such as PROCAM have utilised a broader range of risk predictors than the ‘classical’ factors identified by the Framingham investigators, and in the case of ASSIGN, included for the first time a measure of social deprivation. However these more recent studies were less able than Framingham to measure the natural history of CVD in populations unaffected by drug therapy, a situation that may never arise again.

New resources have been established including large health care databases, allowing ‘prospective’ cohort studies to be conducted based on the follow up of retrospectively identified historical populations, including QRISK and QRISK2.

The range of statistical methods has also expanded, including meta-analytical techniques that allowed the SCORE investigators to combine results from 12 different cohort studies. This process is ongoing, and has included the development of new models of pattern recognition including artificial neural networks. Such models might become more relevant in situations where targeting of therapies is based on a broader, context-dependent definition of CVD risk, and not purely upon independent risk



factors. Trends in health care policy defined in the guidelines of the past decade are moving in this direction, compared with the original aims of the Framingham investigators. We now know the relative importance of the modifiable CVD risk factors (blood pressure, serum cholesterol, tobacco smoking and other lifestyle factors), and effective interventions have been developed to reduce them. The current priority is to target such interventions efficiently towards those at greatest overall risk.

Despite progress in risk *estimation*, cardiovascular risk *reduction* is a more challenging area that includes not only quantitative measures but also qualitative and ethical aspects to be discussed in the next chapter.

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## **Chapter 3: Ethics of cardiovascular risk reduction**

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### **3.1 Introduction**

This chapter explores the ethical issues related to cardiovascular disease prevention: the use of NHS resources to prevent rather than treat disease; the identification and ‘labelling’ of individuals at risk; the issue of personal responsibility for health; and the use of personal information to identify risk. Some of these are specific to cardiovascular disease. Others apply more generally in health care.

### **3.2 Ethics of disease prevention: ‘turning people into patients’**

The first issue concerns the basic principle of disease prevention: can this activity justifiably be resourced in a world where established, manifest disease is still commonplace? Is there an ethical basis for preferring or prioritising a preventive approach over an approach based on treatment of symptomatic disease, or vice versa?

The apparently self-evident wisdom of ‘prevention rather than cure’ is identified as a theme in the in-depth interviews with members of the public discussed in Chapter 8 and reported in the Appendix. However this view is not universally accepted. Iona Heath argues that the National Health Service’s first priority should be to treat those who are suffering before those who may suffer in the future. She defends the notion of a ‘National Sickness Service’ (1) and has suggested a levy on preventive drug therapies in industrialised countries to alleviate established health problems in the developing world (2). Her objection to preventive medicine is primarily based on the moral imperative to treat those who are actually suffering now before those who may (or may very well not) suffer in the future. But she also argues that people living in the

developed world would actually feel better if *less* money were spent on their preventive health care.

This position aims to protect healthy individuals from the potentially detrimental effects of the disease label, i.e. from ‘turning people into patients’(3). However UK policy since 2000 moved in the opposite direction. People ‘at risk’ of cardiovascular disease were to be treated with the same priority (in terms of identification, monitoring and follow up) as those with established, symptomatic disease (4, 5). From a medical perspective this is justified because people are identifiable on the basis of risk factors whose risk of serious cardiovascular events is comparable to those who already have clinical manifestations of the disease. The underlying pathophysiology supports this. Coronary atheroma may predate the onset of an acute event by years, as the development of atheroma is a different process occurring over a much longer timescale than the acute thrombosis that produces a myocardial infarction. People identified as ‘at risk’ of cardiovascular disease may already have established atheroma and from a biomedical perspective have an established pathological disorder that is not yet manifest clinically. This is conceptually distinct from the situation in which risk factors are identifiable but *not* associated with abnormal pathophysiology, such as those at risk of accidents due to risk taking behaviours. A similar distinction might be made between those at risk of prevalent undiagnosed diabetes, a situation that is known to be associated with occult diabetes specific complications and those at risk of future, incident diabetes, which is not. Acute cardiovascular events include potentially lethal myocardial infarction and stroke (from which recovery may be only partial), and sudden death. However a preventive approach involves the treatment (typically with drugs) of people with no symptoms, requiring monitoring and follow up. Heath may be untypical in the strength of her dislike of preventive care, but a concern over the medicalisation of healthy people attracts wider support (3). This is discussed in detail by John-Arne Skolbekken in a book chapter entitled *Unlimited medicalisation? Risk and the pathologisation of*

*normality* (6). Whilst there may be well-recognised detrimental effects of preventive medicine (including the side effects of drugs, the risks associated with screening procedures, and the anxiety created through screening or monitoring processes), a further potential detriment is the wider effect on both individuals and society of a prevention oriented culture. “Turning people into patients” may not only affect self-image but also the perception of others, with (for instance) implications for life insurance premiums. In addition to these issues, Getz et al discuss the impact on the treatment of established disease from pressure on clinicians to address preventive issues opportunistically during consultations, and question the ethics of this approach (7). Interestingly, these authors specifically mention the use of reminders designed to identify preventive health needs in this environment and their potentially detrimental effect on patient autonomy. This area of care is to be explored in depth in the next chapter. But the next question concerns the implications of successfully identifying risk for clinical behaviour and health service priorities.

### **3.3 The ‘Rule of Rescue’**

The ‘Rule of Rescue’ (RR) is the principle that it is justifiable to spend more per quality adjusted life year (QALY) on treating *identifiable* individuals at high risk of avoidable death or serious illness than on smaller reductions in risk among a larger number of non-identifiable individuals in a population (8). We may be confident that a programme of preventive care, such as statin therapy to an at-risk population for cardiovascular events will save lives and reduce morbidity, and we may be able to quantify this utility gain with reasonable accuracy. But we cannot identify which individuals’ lives will benefit, i.e. those who would die or have a cardiovascular event without the treatment. The ethical dilemma arises because the RR conflicts with traditional cost effectiveness analysis (CEA), through which decisions should always optimise overall utility measured in QALYs. Meeting the immediate needs of a high

risk, identifiable individual may be less cost effective than treating or preventing illness in a larger number of less identifiable individuals, but may in practice be justified through the RR. The term RR was originally coined in 1986 by Jonsen (9), and tends to be used when the situation is urgent (preventing carefully balanced decisions over the pros and cons of rescue), distressing (eg the 'buried miner' scenario), well publicised (eg appearing in the mass media), and critical to life or death so that rescue might make all the difference to the outcome (eg the child dying of liver failure needing a liver transplant).

The RR suggests that rescue is attempted even when the overall utility gain will probably be less than if resources were committed in other directions (where the beneficiaries are not identifiable), and even if the risk of death of the rescuers outweighs the survival prospects of the victim. The RR may also influence decision making in less extreme scenarios. The 'rescue' may involve a treatment whose denial would seem unethical even though the cost is difficult to justify on the basis of CEA.

The RR is said to have operated in the Oregon priority setting exercise described by Hadorn (10) and discussed by McKie and Richardson (8). Based on the expected impacts of various treatments for a range of medical and surgical conditions, a priority list was drawn up broadly based on CEA. In several cases life saving emergency treatments (eg for ectopic pregnancy or appendicitis) received a lower priority to more mundane interventions (dental caps for pulp exposure and splints for temporomandibular joint disorder respectively). The situation was resolved by considering and prioritising emergency situations separately. This is suggested by Hadorn to be an example of the Rule of Rescue in practice. The RR in this situation was applied to resolve an otherwise ethically untenable position: the out-prioritising of life threatening emergency treatments by treatments for much less serious and certainly not life threatening conditions.

Hope considered six potential arguments in favour of the RR, and concluded that none were sufficiently powerful to justify its use in rationing health care. However his

discussion does not include the less measurable effect of people believing they belong to a sufficiently compassionate society that their own rescue would be attempted in such circumstances. This aspect of the RR is discussed in detail by McKie and Richardson (8), who also conclude that the RR conflicts with CEA, and is difficult to justify ethically. However, whilst recognising that being 'identifiable' is not a morally relevant ground for discrimination, they suggest that:

*'...the evaluation of health services is not simply a technical matter but a quintessentially ethical endeavour, and that in complex societies with divergent values there may be a range of considerations that may "trump" the utilitarian rationality that is implicit in cost effectiveness analysis.'*

Such considerations perhaps include the detrimental effects of 'labelling' in people treated with preventive therapies discussed earlier (6), an issue that does not apply to 'rescue' scenarios. Many if not most people accepting preventive treatments will not benefit in terms of hard outcomes, whilst a proportion may suffer the negative consequences. But Hope suggests that a society that neglected opportunities to prevent future anonymous deaths would be at least equally uncaring as one that refused treatment to an identifiable individual at high risk of immediate death.

### **3.4 Individual choice versus population benefits**

In addition to the issue of labelling individuals who may or may not benefit from preventive care, the necessary resource commitment has implications for the viability of the health service itself, which may risk overload through the need to identify, assess, treat and follow up a substantial proportion of the population. Getz et al (11) demonstrate the high proportion of the Norwegian population whose cardiovascular

risk profile was adverse in some way according to European guidelines (76% of those over 20 years). Some of this adverse risk is attributable to lifestyle factors that are not necessarily within the remit of clinical health care, but they discuss the likely effect on the adherence of clinicians to such guidelines given this high prevalence.

In a review article in the journal *Nature* Zimmet, Alberti and Shaw claim that “One of the myths of the modern world is that health is determined largely by individual choice” (12). They consider sedentary lifestyle, overly rich diet, and obesity to be to a large degree the consequences of the modern environment. They make a particularly clear appeal for internationally co-ordinated preventive measures to curtail the rising prevalence of ‘diabesity’ and associated vascular disease in the developing world. This contrasts sharply with Heath’s emphasis on treating ‘the sick’ not just in preference to but almost to the exclusion of disease prevention discussed earlier (1, 2). However, the need to address lifestyle factors at a public health level may be a common ground. The question then becomes: to what extent should individuals be targeted for more personally tailored risk assessment and reduction interventions?

Targeting on the basis of absolute cardiovascular risk, discussed in Chapter 2 may lead to the prioritisation of individuals who are unwilling to change their lifestyle above those who have succeeded in doing so. This effect applies particularly to smoking, the most important modifiable cardiovascular risk factor, but also to serum cholesterol and blood pressure, which are also affected by lifestyle choices. Current policy generally leads to targeting of smokers for lipid lowering therapy in preference to those who have succeeded in quitting, as their estimated risk is higher. Some find this approach questionable (13). However, as smoking (and other adverse lifestyle issues) is more prevalent among disadvantaged groups, health inequalities are likely to be amplified should this policy be reversed.

Marteau and Kinmonth discuss the implications of an ‘informed choice’ approach towards cardiovascular risk screening (14). Such an approach is recommended by the National Screening Committee but is different from the

traditional public health approach described in their paper, in which less information is provided to the person screened, and the needs and opinions of individuals are not considered in offering the screening test. Screening programmes may be beneficial at the population level, but only a few individuals will benefit, whilst some may actually be harmed. An informed choice approach, in which the possible adverse outcomes as well as the possible benefits were discussed prior to the individual consenting to participate might filter out many of the poorly motivated, including those with adverse lifestyle factors. The authors make the case that whilst this approach may not achieve the maximum public health benefits, it should make the interventions more effective among those consenting. However they also recognise the potentially adverse effects on health inequalities.

### **3.5 Patient decision making and informed consent**

Whether better-informed patients choose the lifestyle options recommended by the medical profession has been questioned (15). If not, more emphasis on informed choice might in fact backfire as a means of achieving public health gains. In primary care consultations (an environment where decisions about screening and risk frequently take place), Ford et al found in an observational study that the ability of doctors to meet patients' preferences for involvement was very variable (16).

Kinmonth, Woodcock, Griffin et al (17) undertook a randomised controlled trial of patient centred care in newly diagnosed type 2 diabetes (trailing an intervention that trained general practitioners and practice nurses in patient centred consulting techniques). After 12 months, they reported improved treatment satisfaction, wellbeing, and communication with the doctor for those in the intervention arm. However there were detrimental effects on some outcome measures (including body mass index and triglycerides concentrations), and no effect on HbA1c levels. It appeared that an emphasis on patient centred care risked losing focus on risk factor control. We can not

perhaps assume that increasing patient involvement in decision making will achieve the outcomes we might desire as health professionals.

The process of reducing cardiovascular risk may depend on an understanding of the concept of 'risk' that is not necessarily shared between individuals, health professionals, and others, raising further ethical issues. Patients may be unaware that information collected during routine care may at a later date be used to make judgements about their risk of different conditions. This might then affect not only individuals' self image but also their life or health insurance payments. Those without known CVD may currently have no 'disease label' although many who are found to be at risk will have a diagnosis of hypertension, and be on medication for it. A further issue has recently been highlighted by Mangin et al (18), specifically related to the extension of cardiovascular risk reduction to the elderly population. By reducing cardiovascular mortality in elderly people we may be increasing their risk of dying of something they might consider less preferable eg cancer. The PROSPER trial (19) tested the effects of pravastatin on cardiovascular outcomes in people without cardiovascular disease aged 70-82 years followed for an average of 3.2 years. The primary endpoint was reduced significantly (Hazard Ratio 0.85, 95% CI 0.74-0.97) and this was interpreted as a success for the use of statins to prevent CVD in older people. However, the reduction in cardiovascular mortality was offset by an increase in cancer diagnoses in the intervention arm. This effect is unlikely to be a toxic effect of the statin (as it was not evident in a meta-analysis of statin trials conducted by the PROSPER authors). It appears to represent, as Mangin et al suggest, a case of changing the cause of death without reducing overall mortality. Patients might expect to be informed of this effect before starting a statin at this age.

These issues also have implications for clinicians. Good practice in primary care is to record the diagnosis or the clinical indication for each prescription. This therefore requires the application of an electronic code in some form indicating that the person is at raised risk of cardiovascular disease. Without such an entry the clinician is



risking criticism if there is a problem such as an adverse reaction to the medication, as the justification for its use may not be clearly supported in the medical record.

### **3.6 Absolute or relative cardiovascular risk?**

In the case of cardiovascular disease, a policy of targeting people on the basis of raised *absolute* risk will tend to result in a focus on older people whose major risk factors (eg age itself) may be un-modifiable (13). However, this issue relates to that discussed in the previous chapter over whether modifiable (and particularly causative) factors should be allowed to dictate policy over cardiovascular risk reduction.

Those at higher absolute risk are generally likely to benefit more in terms of absolute risk reduction, although their risk factors may be less modifiable. An alternative policy of targeting people on the basis of raised *relative* risk (relative to age- and sex-matched peers) offsets this problem, but it is then more difficult to justify any adverse consequences of being identified (labelling, side effects of medication) as the reduction in absolute risk may, in the short to medium term, be very small, producing a very high number needed to treat for one prevented cardiovascular event. In cardiovascular disease prevention, where disease risk may accrue over decades, the lifetime risk of a serious event may only be reduced by a treatment schedule carried out over a similar timescale, and there is a risk of ‘missing the boat’ if preventive treatments are withheld until the absolute risk is raised to the usual threshold.

### **3.7 Ageism and the Fair Innings Argument (FIA)**

The ethics of extending cardiovascular prevention to older age groups is worth examining further. The 2005 JBS2 guideline (5) advocated no upper age limit for primary prevention, and suggested “a comprehensive cardiovascular risk assessment in all adults aged 40-80 years who attend their general practitioner, or other member of the primary care team, for whatever reason.” Apart from the issues discussed earlier in

this chapter, removing the upper age limit may result in treatment that is less robustly supported by research evidence than in younger groups, so that problems such as reactions to medication (or drug interactions that are commoner in older people) become more difficult to justify. More recently, the NICE CG67 guideline on Lipid Modification (20) reinstated the 40-74 year age group for targeted CVD prevention originally recommended in the 2000 CHD National Service Framework (4). However people starting preventive drug therapies before the age of 75 will continue on them indefinitely according to all of these guidelines. Behind this debate lies the issue of whether people who have lived to average life expectancy should be offered life-prolonging therapies at the public's expense, i.e. do they *have a right to* this investment, or should they simply accept that they've had 'a fair innings'?

The Fair Innings Argument (FIA) has been used to defend the preferential allocation of treatments to younger rather than older people when resources are limited and other factors are equal. According to the FIA, elderly people have had their 'fair share' of life and have less right to access finite resources to extend what time they have left compared with younger people. The FIA is supported by the Judeo-Christian 'three score years and ten' as the natural human lifespan [Psalms 90:10, King James Version]:

*The days of our years are threescore years and ten;  
and if by reason of strength they be fourscore years,  
yet is their strength labour and sorrow;  
for it is soon cut off, and we fly away.*

In 1973 the epidemiologist Sir Richard Doll argued that instead of attempting to increase the span of life we should "aim to reduce mortality at young ages and to relieve disability at old." (21). Monitoring the success of the health service should focus on "the trend in age-specific mortality under 65 years of age and the trend in

prevalence of physical dependence thereafter.” He appears to identify 65years as a threshold in health care policy.

Martin Rivlin (22) argues against the FIA, but his case largely concerns age-based rationing in the context of treatment rather than prevention of illness. Doll’s distinction between reducing mortality and relieving disability is less clear now than in the early 1970s due to the development of new preventive interventions. These include not only effective drug therapies for raised cholesterol and blood pressure, but also surgical treatments. Fairhead and Rothwell draw attention to the systematic under investigation and under treatment of elderly candidates for carotid artery interventions (23). Such interventions aim to prevent stroke, a major cause of disability (and not just mortality) in the older population. Increased life expectancy since the early 1970s may have also influenced policy development over cardiovascular risk reduction, leading to an extension to the 65 year threshold identified by Doll (21).

Despite the generally increasing tendency to extend preventive interventions to older people, the FIA still draws support. Lilford highlighted the need for pragmatism particularly in acute situations where decisions have to be made quickly over finite resources (24). Mangin et al (18) do not use the term explicitly, but hint at the same principle, arguing against the active prevention of cardiovascular disease in those ‘who have already exceeded an average lifespan.’ However, as discussed above their concerns are not about ‘fairness’ per se but surround the issues of individual labelling, altering causes of death without reducing overall mortality, and the broader societal effects resulting from the pathologisation of ageing.

### **3.8 Clinicians’ duty of care**

A final ethical issue to discuss surrounds the clinician’s awareness of raised risk (perhaps facilitated by patient-specific electronic data and/or risk algorithms) and his or her duty of care both to make the patient aware of this raised risk and to address it. This

issue is relevant both to the lack of a shared understanding of the ‘risk’ concept and to that of the varying abilities of clinicians to match patients’ needs for involvement in decision making, both discussed above. This problem is explored further in Chapter 8 as it arose during the initial recruitment for the e-Nudge trial. One general practitioner raised the issue of whether the identification of people at risk of cardiovascular disease would entail a duty of care to address the risk that the clinician might not have time to execute at that particular time. Indeed, the e-Nudge software tested through this research identifies in each practice a parallel ‘control’ population that are at equally raised risk but whose potential need for treatment or advice is not flagged up to the practice team. The Warwickshire Research Ethics Committee considered that as this control arm would receive the ‘usual care’ available in the practice (which included recommended primary prevention strategies) the situation was acceptable. The general practitioner concerned was reassured on a similar basis. However, the increasing availability of risk factor data for various conditions is likely to raise further, similar dilemmas for clinicians in the future, as the identification of risk improves both through better data and better algorithms. The quality of the algorithms used to identify risk is also an issue, as some would claim that the Framingham algorithm that is still the current convention is simply not well enough tailored to the modern UK population to be used to inform decision making for cardiovascular prevention (25).

### **3.9 Summary of ethical issues**

The prevention of cardiovascular disease and type 2 diabetes has become a major priority for health care services throughout the world. This has occurred because of rising prevalence (linked in some situations to increasing life expectancy, in others to lifestyle issues), the availability of effective, affordable preventive treatments, and improvements in the quality of health care records, facilitating the targeting of interventions towards those most likely to benefit. However, what might appear to be

an obvious ethical imperative (the offering of evidence based, potentially life saving treatments to an increasingly receptive population) raises a number of ethical problems.

The first 'group' of issues includes patient awareness, the patient's concept of 'risk', the lack of concordance between patients' choices and health professionals' advice, and the patient's personal responsibility for health. This is particularly relevant in cardiovascular disease prevention, as the most effective (but most difficult to maintain) interventions involve personal lifestyle changes such as smoking cessation and weight reduction.

The second group includes the rationing of preventive treatments and our ability as clinicians to adhere to the conventional logic of cost effectiveness analysis. As discussed above, traditional CEA based on the maximisation of overall utility gain is a poor model for instinctive human decision making. It may be 'trumped' by the Rule of Rescue and Fair Innings Arguments whose intuitive appeal to the public, the media, and to many clinicians may override a more rational policy.

Thirdly, a group of issues surrounds the pathologisation of ageing and the potentially detrimental effects of 'turning people into patients,' including its implications for self image and life insurance risk. This is arguably the most important group, particularly where patient awareness of the issues is insufficient to inform individual decision making, and where reducing cardiovascular risk might potentially lead to increased suffering due to the alternative development of even more disabling conditions such as cancer. However, this specific area is not well researched, and whilst touched on in the patient interviews described in Chapter 8, is beyond the scope of this thesis.

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## **Chapter 4: Systematic literature review: Changing clinical practice through patient specific electronic reminders available in the consultation**

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### **4.1 Introduction**

I have drawn on a number of areas of literature to support this thesis. The most important area concerns the effects of electronically generated reminders on the behaviour of clinicians in the consultation environment. Literature searches were initially undertaken non-systematically to support the e-Nudge trial protocol. Most of the citations identified were not included in the formal review described in detail in this chapter, which includes a number of new papers that had not originally been found. This systematic review was carried out in collaboration with Margaret Thorogood and Frances Griffiths. I will first of all explore the background to this piece of work and then describe the methods in detail. The preliminary and final results will then be reported. At the end of the chapter I will also discuss the influence of excluded papers on the overall thesis.

### **4.2 Changing professional practice through electronic reminders**

Automated electronic screen reminders are now a standard component of practice based software in the UK. Their use increased following the introduction of the Quality and Outcomes Framework (QOF) of April 2004. Optional screen message functionality was established in most UK practices from 2005. A later chapter will describe how this impacted on the e-Nudge trial, on the one hand increasing practices' receptiveness to the testing of an alert-generating tool, but also requiring that one of the original six



subgroups of the trial was withdrawn. This was due to the introduction of identical QOF alerts as standard practice in UK primary care. A further subgroup was also later withdrawn due to national developments resulting partly from the e-Nudge trial itself and described in Chapters 8 and 10. But despite their widespread use, screen alert messages and electronic reminders have a mixed evidence base as tools to support health care. This became a very relevant and also topical area of study.

#### **4.2.1 The Shojania 2009 review**

An unpublished Cochrane review protocol (1) that I originally identified (and mentioned in Chapter 1) was replaced by a new review by Shojania et al published in July 2009 (2), by which time our own review was almost completed. Shojania 2009 covered areas that were similar but not identical to our review. The authors commented that previous reviews failed to distinguish between reminders delivered to the clinician *at the point of care* from those delivered in other settings (e.g. by email outside the consultation). This was indeed an important issue that we had identified in designing our own review method. Entitled *The effects of on-screen, point of care computer reminders on processes and outcomes of care*, Shojania 2009 differed from ours in two major respects. Firstly, we chose to include computer generated paper reminders provided that they were displayed at the point of care. Shojania 2009 recognised that such reminders may be as relevant as on-screen reminders and that the matter of greatest importance is whether the intervention is delivered ‘at the point of care’. However, their review title still included the term ‘on-screen’ and a number of articles were excluded on the basis that they were not on-screen reminders (but in fact were paper based). Secondly, we required the computer responsible for generating the reminders to draw on *patient specific* information in the record rather than simply providing ‘best practice’ recommendations for a particular disease condition or prescribed medication. A reminder to monitor full blood count in response to a prescription for methotrexate for instance, would only be included in our review if the

intervention examined the individual patient's electronic record and only generated the reminder if a full blood count had not been recorded within the required time interval.

The conclusions of the Shojania 2009 review were that on-screen, point of care reminders are generally beneficial, but that their effect on provider behaviour is small to modest in the majority of cases. The review was unable to identify specific features of either the reminder or the context that predicted the effect size (2).

Shojania 2009 and Kawamoto 2005 were examined in detail as part of a process (discussed below) through which additional references were identified for our review.

### **4.3 Method for our systematic literature review**

#### **4.3.1 Protocol statement**

In designing this review, we (TH, MT, FG) considered the essential characteristics of the e-Nudge intervention that were of particular interest and which had not been covered in previous published reviews. This included the use of *patient-specific* information held in an electronic record as the basis for electronic reminders, and their availability within the consultation environment. The protocol statement was:

*Can clinical practice be changed by patient specific computer generated reminders available in the consultation?*

#### **4.3.2 Search strategies**

The search strategy was designed prospectively but developed iteratively. An initial PubMed search was conducted on 7.9.07 using the following parameters:

Reminder systems [MeSH] AND (Computer\* [text word] OR Electronic\* [text word])

Limits: Date of publication 1<sup>st</sup> January 1970 to present

Human

English

Major Topic

Randomised controlled trial OR Controlled clinical trial

This returned 87 articles. I combined these with the 38 citations originally mentioned by Kaveh Shojania with 12 duplicates excluded, to produce a list of 113 references.

This list appeared rather short. We considered it likely that other relevant literature would be available and that this original search was too restrictive. The fact that Shojania's papers were only duplicated in 12 instances reinforced this. Whilst controlled trials were likely to provide the most robust evidence of effectiveness, the exclusion of non-controlled trials might have missed potentially important references describing evidence for reminder interventions. (This decision was in fact later reversed as discussed below, but in the process much more literature was examined and this benefitted the review as well as the thesis.) It was also necessary to apply the search to a broader range of databases including social science literature. Following discussion with Samantha Johnson of University of Warwick Library, the following adjustments were made:

1. Remove the 'RCT/Controlled clinical trials' limit
2. Change the search terms to:

Reminder systems [MeSH] AND (Health OR Medic\* OR Clinical) AND (Computer\* [text word] OR Electronic\* [text word])

(Not all of these databases use MeSH terms, in which case Reminder systems was included as a text word or key word).

3. Repeat on the following databases:

- ISI Web of Knowledge (using Science Citation Index Expanded and Social Sciences Citation Index but not the Arts and Humanities Citation Index)
- PubMed
- Medline
- ASSIA
- DARE
- EMBASE
- CINAHL
- HMIC

Continue the limits: Humans, English language, and Publication date 1970-present.

Where possible, 'Health' was an exploded Key word as well as a Text word. 'Clinical' was included both as the Key word 'Clinical Medicine' (exploded) and the text word clinical\*. This search protocol was saved in OVID so that it could be regularly repeated, and email alerts of new entries were set up in ISI Web of Knowledge.

#### **4.4 Initial results**

The searches were conducted on 4.12.07 and the following results obtained (Table 4.1):

Source	Identified	Duplicates	Running total
ISI Web of Knowledge	85	N/A	85
PubMed	353	32	406
Medline	No new references not already included in PubMed		
HMIC	6	2	410
Embase	61	28	443
CRD/DARE	5	0	448
CINAHL	108	43	<b>513</b>

*Table 4.1: Numbers of papers identified, and cumulative total from different source databases.*

The citations were imported into EndNote libraries and then merged as a final combined library. A further manual trawl for duplicates identified 33 more, leaving a running total of 480. Finally, the 113 references from the original search were imported. Of these, 88 were already present, and 25 were included.

New total: **505 references**

The abstracts of these 505 references were examined using the following decision rules derived from the protocol statement: *Can clinical practice be changed by patient specific computer generated reminders available in the consultation?*

#### **4.4.1 Decision rules**

**1. Clinical practice.** This meant the *professional behaviour of clinicians*. Clinicians may be doctors, nurses, health visitors, midwives, chiropodists, or other health professionals but we did not include reminder interventions that only influence administrative or other non-clinical aspects of care. On this basis we excluded articles about reminders that generate recall letters to patients regarding overdue screening interventions or vaccinations.

**2. Patient specific.** The reminders needed to be *patient*-specific rather than simply providing advice on good practice in a specific clinical area. We therefore excluded decision support systems that were not using patient data, or those whose content related simply to a diagnosis but were not otherwise patient-specific. We also excluded reports of interventions that were specific to a diagnostic test (or vaccination) rather than being specific to the patient.

**3. Computer generated.** The ‘reminders’ may be paper-based but must have been *generated using a computer*. They do not have to be visible on the screen but must be readily visible within the consultation environment. A computer generated printed reminder attached to paper notes for use during a consultation would be included provided the other criteria were met.

**4. Available in the consultation.** A clinician must be able to readily access the reminders during a consultation, with little effort. We included reminders that do not appear on the screen automatically, provided they are sufficiently available to (potentially) influence clinical practice in this environment. If the clinician has to actively seek the reminder (eg by opening a new software module) then we excluded the paper.

We continued to specify that only papers published after 1970 would be included. This generally predates the use of electronic reminders in the consultation environment anywhere in the world.

#### **4.4.2 Initial examination of abstracts**

Abstracts of the 505 references were all examined by TH and were distributed between MT and FG (50% each) to identify articles clearly irrelevant to the review.

This process created 4 different categories (Table 4.2):

	Number
Both agreed the reference should be excluded	235
One reviewer wished to exclude but the other to include	83
One reviewer felt unsure but the other wished to include	49
Both agreed the reference should go through to the next stage	138

*Table 4.2: Initial categories of decisions.*

#### 4.4.3 Casting votes

During the next stage a third opinion was obtained on the 132 abstracts where there was disagreement or uncertainty. This process resulted in the following decisions (Table 4.3):

	Number
Excluded from review after casting vote	95
Included in the next stage after casting vote	37
Number already identified in first stage	138
Total included in the next stage	<b>175</b>

*Table 4.3: Casting vote outcomes*

The next stage was to obtain full text pdfs of these 175 articles (all of the original 505 not considered irrelevant by at least two reviewers on the basis of the abstract) and where a paper was excluded, determine the reason for exclusion.

#### 4.4.4 Exclusions based on examining the full texts and exclusion of non-controlled studies

I examined each of the original 175 full text articles, and each was also examined by either MT or FG. During this process the decision to include non-controlled studies was revised. As described above, the initial search had included only controlled trials of

interventions. For the benefit of the thesis I decided to broaden this search and include all types of study, to gain insights into the use and design of similar interventions to the e-Nudge in different organisational contexts. Some of the papers so identified describe the design and development (but not trialling) of such interventions and were therefore of interest. Others test the effects of the intervention using before-after designs so that there is an historical comparator. However during the data extraction process described below we examined a number of such papers that were of poor methodological quality and appeared to have been carried out in an opportunistic, unplanned or even retrospective way. We therefore decided to exclude all uncontrolled trials from the systematic review. This had a considerable impact on the numbers included.

For each excluded paper, a reason was given based on the following categories:

1. **Not related to clinical practice.** This included studies of reminder interventions aimed at patients rather than clinician behaviour, such as letters to patients about overdue vaccination or screening.
2. **Not patient specific.** This group included interventions that simply reminded clinicians about best practice but did not draw on patient specific data in the record, other than perhaps a major diagnosis.
3. **Not computer generated.** One study tested a reminder that required no electronic data. This was excluded under this heading.
4. **Not available during the consultation.** A number of studies tested systems that drew on electronic data but then sent a reminder either to the patient or to a non-clinical professional outside the consultation environment.
5. **Inappropriate type of study.** This exclusion group was a large one, and included all studies that did not have a contemporaneous control group, and also papers describing the development of interventions or providing qualitative analyses, e.g. of acceptability or usability.



**6. Other reason for exclusion.** These included studies where it was not possible to distinguish a patient directed component from a clinician directed component of an intervention. In a few cases, it was not possible to extract the outcome data as no denominator was given (only the proportions), and attempts to obtain the raw data from the article authors failed.

In some cases, a paper could be excluded on the basis of more than one category.

#### **4.5 Re-run of the original searches**

I originally ran the searches on 4.12.07. At the same time, I created an alert in ISI Web of Knowledge to identify subsequent citations and these were sent to me by email on a weekly basis. On 11.2.09 I examined all of these emails and altogether 12 new articles were identified. Of these, one was possibly relevant (Mold JW), and one was a systematic review (Dexheimer (3)) that I also kept and have described above. Both of these were transferred to a new EndNote library.

I was concerned that only one possible study had been identified (as I expected that the number of trials in this area would be increasing over the last decade) and decided to make the other repeat searches more inclusive.

A further search was carried out on 11.2.09 using OVID including MEDLINE, EMBASE and HMIC. It used the following terms:

**Key words:**                      Reminder\$  
  AND Health  
  AND Electronic

**Limits:**                              Years 2007-2009  
  Human

### English language

This produced 34 papers and included the systematic review by Dexheimer, but not the Mold reference. This was therefore added to make 35 references in total.

A further search was then carried out on **MEDLINE**, **EMBASE** and **HMIC** databases via **OVID** using the original search term:

Reminder systems AND (Health OR Medic\* OR Clinical) AND (Computer\* OR Electronic\*) (Limited to publication years 2007-2009)

in the Textword field. This yielded just nine references, three of which were duplicates when uploaded to the EndNote library i.e. a further six references were identified using this apparently less inclusive strategy (but most of the original 34 above were not). After discarding these three duplicates there were 41 references.

For the **CINAHL** repeat search I simply used:

MW Reminder AND MW electronic

and then MW Reminder AND MW computer

(where MW means that the word is in the subject heading)

This returned 13 and then 8 = 21 articles. Six of these were duplicates, giving 56 citations so far.

The **DARE** database was then searched but produced no relevant reviews. At this point we had decided anyway to exclude reviews from our own review although they might still be useful for the thesis if related to electronic reminders. None of the nine returned was relevant.

**ASSIA** was next searched and produced no new citations.

Finally, a more inclusive search was carried out on PubMed using the search term:

Reminder systems [MeSH] (Limited to 1.11.07-12.2.09, Humans, English language)

This returned 125 citations. When combined with the 62 above there were 15 duplicates, giving a final list of 166 references for the updated search.

I then examined all of these 166 abstracts, removing obviously irrelevant articles to find 58 papers of potential interest, from the following sources (Table 4.4):

	Number
PubMed	45
Ovid: Medline/Embase/HMIC	10
CINAHL	11
Duplicates	8
<b>Total</b>	<b>58</b>

*Table 4.4: Initial results of the re-run searches.*

These abstracts were then distributed between Frances Griffiths (FG) and Margaret Thorogood (MT). Disagreements in 14 cases were resolved by the third reviewer, and 8 papers required full text assessment and if appropriate, data extraction. These full texts were then distributed equally between MT and FG and I also examined them. Further rejections occurred and at the end of this process, only three new studies resulting from the re-run searches were identified that were included in the review. These were Lo 2009, Matheny 2008, and Tamblyn 2008.

#### **4.6 Results before final additions**

As a result of the original searches of November 2007 and the updated searches of February 2009, a total of  $175+58=233$  abstracts were identified (out of  $505+166=671$ )

and, following full text examination where necessary, 204 were rejected. The following table gives the numbers of abstracts excluded for the 202 papers for each of six exclusion criteria. In some cases more than one reason was present.

<b>Not related to clinical practice</b>	14
<b>Not patient specific</b>	13
<b>Not computer generated</b>	1
<b>Not available in the consultation</b>	37
<b>Inappropriate type of study</b>	141
<b>Other reason for exclusion</b>	9

*Table 4.5: Reasons for exclusion of 202 initial full papers examined.*

## **4.7 Additions based on other systematic reviews**

I examined the reference lists of other systematic reviews, particularly the two most recent ones: Shojania 2009 and Kawamoto 2005 (2, 4). I was looking for papers relevant to our review that had not been identified so far.

### **4.7.1 Comparison with Shojania 2009**

Of the 29 papers included in the Shojania 2009 review, five were not initially identified in our original 505 papers resulting from the first searches. This was presumably due to the wider search protocol used by these authors, which included search terms such as ‘Prompt’ as well as ‘Reminder’. In all other cases, lack of overlap between this review and ours was the result of inclusion/exclusion decisions. Twelve of the 29 papers in Shojania 2009 were at that point already included in our review. We re-examined nine papers included in this review that we had previously rejected, as well as the five that we had not identified in our 505 originally identified papers. As a result, ten new papers were included (Dexter 2001, Frank 2004, Hicks 2007, Judge 2006, Kralj 2003, Rothschild 2007, Tamblyn 2003, Tierney 2003, Tierney 2005, and van Wijk 2008).

#### **4.7.2 Comparison with Kawamoto 2005**

I looked closely at this review as it was published quite recently and overlapped significantly with ours. However this group had included a wider range of CDSS systems and the majority of their papers were not in fact relevant for us. Their review identified a total of 88 papers, but aimed primarily to identify factors predicting the effect of CDSS interventions rather than actually measuring the effect size itself. As a result, seven new papers were included in our review (Burack 1996, Burack 1998, Chambers 1991, McDonald 1980, McDonald 1976, McDonald 1984, McDowell 1998).

### **4.8 Final results**

A number of papers included descriptions of interventions, or of analyses that were not clear enough to the three reviewers to enable data extraction. In twelve cases I contacted the original authors by email for clarification. Eight of these resulted in responses but in 4 cases the paper was withdrawn as it became apparent that it no longer met the inclusion criteria.

The result of this final stage was that 41 studies were included in our final list (5-45). These studies included a range of significantly different analytical approaches affecting the interpretation of outcomes.

#### **4.8.1 Issues affecting interpretation**

Some studies included more than one type of intervention e.g. clinician directed *and* patient directed, or consultation based *and* telephone reminders. In these cases we only included data related to the intervention relevant to our review. Studies had been excluded where it was not possible to separate the clinician-directed effect from a patient directed effect on the outcome, as we were only interested in the former. Other studies involved multiple reminders (e.g. vaccination, screening tests, etc) and it was straightforward to combine the results into aggregate figures. This was a similar

process to that actually provided in the reports of other papers, where the overall response to multiple reminders was given. In two cases (Tamblyn 2003, and van Wijk 2008), the study results needed to be subdivided into two sub-studies as aggregation would have been inappropriate. In the case of Dexter 1998, there were three slightly different interventions that were all relevant to our review, with one control arm. Following advice from Dr Simon Gates, we divided the control data in this study by three (both numerator and denominator, giving effectively the same control odds) and entered each intervention as if it were a separate study. This avoided overweighting of these studies in the meta-analysis. One study (Eccles 2002) was not included in the meta-analysis for reasons discussed below.

Based on this interpretation we identified a final list of 44 comparisons from the 41 papers. A list of the included studies is given in Table 4.6 along with some descriptive details and comments.

## **4.9 Data extraction**

To extract the necessary data from these papers, a template form was developed iteratively through trialling on the first few papers followed by review. The third draft became the version used and is given in the Appendix. Whilst this form includes a row for 'Baseline numerator and denominator,' we used odds ratios based on the outcomes alone rather than the change from baseline. As recommended by the Cochrane Handbook for Systematic Reviews of Interventions (46), this form was completed by two reviewers for each paper. This enabled us to identify errors of interpretation. Where these occurred a consensus was obtained through discussion or by referring to the third reviewer.

<b>Study</b>	<b>Country</b>	<b>Setting</b>	<b>Area of care/target behaviour</b>	<b>Comments</b>
<b>Bates 1999(6)</b>	USA	Tertiary care hospital inpatients	Diagnostic tests – identifying redundant tests	Randomised by internal identification number (as in e-Nudge)
<b>Burack 1996(7)</b>	USA	Large Health Maintenance Organisation in Detroit	Mammography screening in women overdue a mammogram	For the physician directed intervention only women who actually visited were included in the analysis
<b>Burack 1998 (8)</b>	USA	Large Health Maintenance Organisation in Detroit	Cervical cancer screening in women due a Pap smear	As above, eligible women who did not attend the clinic were not included in the analysis
<b>Chambers 1991 (9)</b>	USA	University based family practice centre	Completion of influenza vaccination in eligible people	Positive evidence that reminders were not contaminating the control arm
<b>Dexter 1998 (10)</b>	USA	Academic primary care practice affiliated to an urban teaching hospital	Discussions about advanced directives	Divided into three comparisons in our RevMan analysis, so the control data divided into three for each comparison to avoid over-weighting
<b>Dexter 2001 (11)</b>	USA	Inpatient wards of teaching hospital	Preventive care: pneumococcal and influenza vaccination, subcutaneous heparin, aspirin	28% were hospitalised more than once during the study
<b>Eccles 2002 (12)</b>	UK	General practice in UK	Multiple process of care outcomes related to management of angina and asthma	Unable to extract data as no primary outcome identified
<b>Fillipi 2003 (13)</b>	Italy	Italian general practice	Anti-platelet prescribing for patients with diabetes over 30 years with one other CVD risk factor	Optional intervention, general practitioner had to activate it
<b>Frank 2004 (14)</b>	Australia	Australian general practice	Multiple reminders for preventive activities	Data from all reminders aggregated in our analysis
<b>Hicks 2007 (15)</b>	USA	Primary care practices	Management of hypertension	Clinical outcome, not significant.
<b>Judge 2006 (16)</b>	Canada	Academically affiliated long term care facility	Prescribing safety issues	Example of analysis by reminder opportunity

<b>Kenealy 2005 (17)</b>	New Zealand	Primary care practices	Screening for diabetes in people over 50 years with no blood glucose in the past 3 yrs	Contacted the author for accurate denominator data
<b>Kralj 2003 (18)</b>	USA	Community oncology practices	Prescription for erythropoietin to patients with cancer and Haemoglobin <12g/dL.	Significant difference between control and intervention arm at baseline
<b>Krall 2004 (19)</b>	USA	Kaiser Permanente Northwest	Prescription of aspirin in eligible patients	Single off-line data analysis after a month to detect patients still eligible for an alert
<b>Kucher 2005 (20)</b>	USA	Inpatients on medical and surgical wards	Identification of patients at risk of deep vein thrombosis or pulmonary embolism	Positive result from a clinical outcome study (only example in this review)
<b>Litzelman 1993 (21)</b>	USA	Academic primary care internal medicine practice	Cancer screening investigations (Pap smear, mammography, faecal occult blood)	Reminders need a response to indicate intended actions
<b>Lo 2009 (22)</b>	USA	Academic teaching hospitals, community hospitals and outpatient clinics	Recommendations for baseline test when prescribing new medication	Similar to Matheny 2008 but relates to baseline rather than ongoing monitoring tests
<b>Matheny 2008 (5)</b>	USA	Academic teaching hospitals, community hospitals and outpatient clinics	Reminders for arranging monitoring tests for ongoing medication prescriptions	As above – very similar to Lo 2009
<b>McCowan 2001 (23)</b>	UK	UK general practice	Asthma guidelines with reminders including the need for asthma review	Primary care consultations identifiable as the primary outcome, but there were many outcomes
<b>McDonald 1976 (24)</b>	USA	Hospital diabetes clinic	Reminders to order tests or change therapy	The two reminder types were combined in our analysis.
<b>McDonald 1980 (25)</b>	USA	Hospital General Medicine clinic	Computerised management rules predominantly related to prescribing	The two active interventions (which were very similar) were aggregated in our analysis as suggested was appropriate in the paper



<b>McDowell 1989a (26)</b>	Canada	Family Medicine Centre at civic hospital	Blood pressure measurement	Two other arms included in this study were excluded from this review
<b>McDowell 1989b (27)</b>	Canada	Family Medicine Centre at civic hospital	Screening for cervical cancer by Pap smear	Used the intention to treat data in our analysis
<b>Murray 2004 (28)</b>	USA	Academic primary care Internal medicine practice	Treatment suggestions for management of uncomplicated hypertension	Also included a Health related quality of life secondary outcome
<b>Overhage 1996 (29)</b>	USA	Inpatient general medical ward	Related to multiple preventive interventions	Reminders were both paper and on-screen
<b>Overhage 1997 (30)</b>	USA	Inpatient general medical ward	Prescribing reminders	Immediate compliance rather than 24 hour outcome used in our analysis
<b>Rosser 1991 (31)</b>	Canada	Family Medicine Centre at a civic hospital	Multiple preventive interventions (screening, vaccination, assessment)	Two other interventions arms (letter and telephone reminders) not relevant to our review
<b>Rosser 1992 (32)</b>	Canada	Family Medicine Centre at a civic hospital	Tetanus vaccination reminders	Thirty-eight consultations monitored to detect unrecorded vaccinations
<b>Rossi 1997 (33)</b>	USA	Primary care providers	Reminders to change patients with hypertension taking calcium channel blockers to alternative drug	Quality assured through pharmacy check and check on patient records
<b>Rothschild 2007 (34)</b>	USA	Academic medical centre with emergency department and inpatient beds	Reminders concerning inappropriate orders for transfusion products	All orders independently checked for appropriateness and inter-rater agreement measured
<b>Safran 1995 (35)</b>	USA	Hospital based outpatient clinic	Guidelines on management of HIV infection	Analysis include binary and continuous measures of the same outcome
<b>Sequist 2005 (36)</b>	USA	Network of outpatient clinics, community and	Management of diabetes and of coronary heart disease	Aggregated data extracted for RevMan

		teaching hospitals		
<b>Shea 1995 (37)</b>	USA	Large urban hospital	Screen messages giving estimated discharge date for diagnostic groups	The only continuous outcome study (length of stay) in our review
<b>Tamblyn 2003 (38)</b>	Canada	Canadian primary care	Prescribing issues	Data extracted and added to RevMan separately for prescribing and discontinuation outcomes
<b>Tamblyn 2008 (39)</b>	Canada	Canadian primary care	Reminders to identify prescribing problems	One arm required the clinician to actively view the alert when they considered it relevant. We called this the control arm.
<b>Tape 1993 (40)</b>	USA	Academic Internal medicine clinic	Range of screening (mammography, Pap smear, thyroid function, faecal occult blood) and vaccination reminders	Aggregate of all reminders used in our analysis
<b>Tierney 1987 (41)</b>	USA	Academic primary care general medicine clinic affiliated to urban hospital	Diagnostic tests – reminding user of the number and timing of previous requests for the same test	Only analysed those who visited
<b>Tierney 2003 (42)</b>	USA	Academic primary care group practice	Cardiac care suggestions	The pharmacist intervention was not included as we did not consider it to be delivered at the point of care
<b>Tierney 2005 (43)</b>	USA	Inner city academic General Medicine clinic	Prescribing suggestions related to care of patients with asthma or COPD	As above for Tierney 2003
<b>van Wijk 2008 (44)</b>	Netherlands	Dutch general practice	Screening and prescribing reminders	Data for screening and for treatment extracted and added to RevMan separately
<b>White 1984 (45)</b>	USA	Inpatients in a teaching hospital	Reminders concerning risk of digoxin toxicity	We chose the ‘alert day’ as the reminder opportunity denominator

*Table 4.6: Outline of the 41 studies included in the systematic review.*

## **4.10 A narrative synthesis**

Before attempting to synthesise the quantitative data provided by these studies I will discuss some of the qualitative aspects. These provide at least as much support for this review and for the thesis.

### **4.10.1 Methodological quality**

A small number of studies were excluded because the data on denominator values was unavailable both in the trial report and from the investigators. The studies excluded on this basis tended to be older ones, several dating from before the 1990s. This partly reflected difficulties in tracking down original datasets, and in one case the principal investigator was deceased. However, it may also reflect an increased awareness in more recent times of the necessity to facilitate future meta-analysis. Meta-analysis was established during the mid to late 1980s (47), and requires sample size data (and not just proportions) to weight the contribution of a trial to the overall result.

A further quality issue that influenced the final selection was the issue of before/after trial designs. We originally decided to include such trials in order to widen our sample, but some of these studies were of particularly poor quality, leading to a reversal of this decision. Some appeared to have been carried out following either the introduction of a new CDSS tool or a newly established health policy or initiative. The study would then compare what was happening since a given point in time with what had happened (in retrospect) prior to that time point. It is particularly in the setting of shifting health policy that a controlled study with parallel, contemporaneous trial arms is required to separate the effect attributable to the intervention from other factors.

Very few of our included studies were supported by published trial protocols that described the trial design and defined its outcomes. They varied considerably in the attempts made by investigators to quality assure the data collection processes and remove potential sources of bias. However, we decided that peer-reviewed publication

was the minimum acceptable quality standard and this approach removed any of our own biases or preferences from the selection process.

#### **4.10.2 International issues**

In addition to the need to clarify denominator values with trial investigators, I needed to contact several researchers (all from the United States) simply as a result of my initial lack of familiarity with North American processes of care. Study reports sometimes make assumptions about the readers' understanding of the prevailing health care context, and clarification was required on several occasions. UK National Health Service consultations (and their associated software environments), particularly in primary care, are different in certain important respects to the US system in otherwise similar contexts. These differences might determine whether or not a reminder intervention was delivered 'at the point of care' as we interpreted the term. This issue reinforced my later need to describe the e-Nudge intervention in sufficient detail for an international readership.

#### **4.10.3 Overall results**

The majority of the studies produced positive results, although this was by no means universal. In several cases the trial reported results of borderline statistical significance (eg Judge 2006), or of non-significant results (e.g. Burack 1998, Eccles 2002, Hicks 2007, Matheny 2008, Tierney 2003 and Tierney 2005). The trials varied very significantly both in the particular aspect of care under study, and in their scale, some involving relatively few patients within one general practice (e.g. Dexter 1998) and others trialling interventions applied to large populations randomised automatically (e.g. Tamblyn 2003), in ways similar to the e-Nudge trial described later in this thesis.

The impression gained from examining these reports supported the conclusions of the existing reviews already described: that the impact of reminder interventions on clinical behaviour was generally positive, but unpredictable, inconsistent, and probably

context dependent. However, specific aspects of the context predicting success were difficult to identify. Financial issues were rarely discussed as contextual factors, other than the health economic implications (for instance laboratory costs) of test ordering behaviour. The specific issue of ‘payment by results’ to practitioners and the effect of this factor in determining responsiveness to reminder interventions is almost absent from the literature that I examined. However, conversations with North American colleagues made me aware that such factors are important in the US, even if not quite so directly as under the UK’s Quality and Outcomes Framework. Their lack of coverage does not necessarily mean that they are unimportant. This reinforced the need to discuss such factors openly in the e-Nudge report that resulted from my own reminder intervention trial described later.

#### **4.11 RevMan analysis**

Data extraction using the paper forms was followed by entry into RevMan (Version 5.2). All but one paper used binary outcomes and I set RevMan to analyse odds ratios using the Mantel-Haenszel (MH) method with 95% confidence intervals. The MH method is the default option in RevMan. Inverse variance is an alternative that was introduced in the most recent fifth version, and the difference between the two methods is very slight (46). This difference affects the way that each study is weighted by the software. Inverse variance gives a weight to each study that is proportional to the inverse of the variance of the treatment effect of that study (so that larger studies with lower variance are given proportionally more weight). The MH method uses a slightly more complicated algorithm for defining weights described in Friedman, Furberg and DeMets (48). I checked the odds ratios derived in our review using the inverse variance method and none of them were significantly different.

An early issue arising from this analysis was that of heterogeneity. I questioned whether or not the individual studies were sufficiently comparable to enable a meta-

analysis that might add to the qualitative analysis discussed above. If not, could I identify one or more subgroups that might permit such a synthesis?

#### **4.11.1 Heterogeneity**

The Cochrane Handbook (46) identifies three major sources of heterogeneity affecting studies subjected to meta-analysis. The first is *clinical diversity*, resulting from variation in the participants, interventions, or outcomes studied. The second is *methodological diversity*, which reflects variation in trial design (even if all are randomised controlled trials), or factors affecting the risk of bias. The third is *statistical heterogeneity*, which refers to differences in measured intervention effects. Statistical heterogeneity is assumed to be the result of clinical and/or methodological diversity, and is suggested by forest plots displaying varying effect sizes whose confidence intervals overlap poorly. Such a finding precludes a meaningful meta-analysis.

#### **4.11.2 Random effects or a fixed effect?**

I considered whether the effect that we were investigating was itself a distributed quantity, or whether the observed variation in its effect between studies was purely due to measurement error, from whatever source. Each individual study represents an independent measurement of the reminder effect on clinician behaviour. Are the studies separately sampling an effect of unvarying magnitude (like independent measurements of the height of Big Ben), or are they measuring a distributed variable (such as the average height of all the buildings of central London)? We discussed whether to use a fixed effect or random effects model for our analysis, which is the implication of this distinction. We believed that it was meaningful to assume a broadly common effect influencing clinicians in all of the different trial conditions, but we did not assume that this effect would be the same in all contexts. We concluded that the effect was likely to vary naturally in different settings and follow a distribution rather than produce the same effect in all study scenarios. Variation in the measured effect would not be due

solely to clinical or methodological diversity. It would in fact be a natural property of the influence of reminder interventions, and a random effects model would therefore be appropriate.

#### **4.11.3 Subgroups of identified papers**

The forest plots (Figures 4.1-4.4) demonstrate a degree of statistical heterogeneity in our sample of studies, with quite wide variation in effect size and confidence interval. This was confirmed through the overall  $\text{Tau}^2$  value of 0.20 for all binary process outcome studies. This index is appropriate for measuring the heterogeneity of studies under a random effects assumption.

I attempted to identify useful subgroups of study that shared common features. The primary aim of this exercise was to identify categories of intervention that were more likely to be associated with positive outcomes or larger effect sizes, but I was also interested in reducing heterogeneity. No two studies examined exactly the same process, although some were very similar, and there were examples where two different areas of care using essentially the same software had been trialled and reported separately.

Subgroups among the papers included those based on statistical form of the outcome measure (e.g. binary, continuous), whether designed to influence process outcomes or clinical outcomes, and the area of care under study. Finally, a distinction could be made based upon the unit of analysis, and this struck me as the most important means of identifying subgroups (or perhaps just one subgroup) for which meta-analysis might be particularly meaningful. I identified the studies that used the 'reminder opportunity' as the denominator, i.e. studies that reported the proportion of opportunities for a clinician to respond to a reminder that resulted in the target behaviour. By identifying the subgroup of studies sharing this unit of analysis, I was hoping to measure the *efficacy* of reminder interventions to influence the immediate behaviour of clinicians (i.e. within the point of care encounter). The other unit of

analysis, based on population proportion outcomes, would be comparable with the more pragmatic studies of *effectiveness* designed to demonstrate the ultimate benefit of such interventions at the population level. These studies did not measure how many times (if any) the clinicians had received a reminder. A patient might have visited the practice many times during the study (to trigger a reminder each time), or not at all.

#### **4.11.3.1 Binary outcomes versus continuous outcomes**

Binary outcomes related either to compliance with reminder suggestions, i.e. appropriate clinician response to the reminder, or achievement of target outcome as a result of clinician response to the reminder (such as screening test undertaken or recommended drug prescribed). However, only one study reported a continuous outcome: length of hospital stay (37). This was therefore not a useful distinction.

#### **4.11.3.2 Process outcomes versus clinical outcomes**

This distinction was important, but in fact all of the included papers involved process outcomes, with the exception of Kucher 2005, which measured rates of venous thrombo-embolism (20), and Hicks 2007 (15), which measured the achievement of blood pressure control. This highlighted the paucity of evidence based on clinical rather than process outcomes. As discussed in Chapter 1, Montgomery and Fahey (49) and Tu and Davis (50), had reached a similar conclusion. Another difficulty was that Hicks 2007 measures the effects of reminders on the successful achievement of blood pressure control, whilst Kucher 2005 measures rates of venous thrombo-embolism. In the first case, an odds ratio greater than 1 favours the intervention, whilst in the latter the odds ratio was less than 1, reflecting successful reduction of thrombosis risk.

#### **4.11.3.3 Area of care**

The following areas of care served as useful categories, although there was significant overlap with some reminders covering more than one area:



- Vaccination
- Screening
- Prescribing
- Monitoring or diagnostic tests
- Condition specific reminders (i.e. multiple reminder systems related to a single diagnosis such as asthma or diabetes, and perhaps including prescribing and lifestyle issue reminders)
- Other or multiple reminders (several papers described software interventions reminding clinicians about numerous unrelated actions).

#### **4.11.3.4 Unit of analysis**

Different definitions used for the denominator populations in the trial outcomes provided a particularly important barrier to data synthesis. I was interested primarily in the behavioural response of clinicians to a reminder message, and the most useful examples were those in which the unit of analysis was the reminder message opportunity itself. For instance, if patients were randomised into two arms (intervention and control), one arm receiving messages and the other not, then the most useful studies (in terms of quantitative synthesis) might be those that were able to give the number of opportunities to influence the clinician as the denominator (i.e. the number of actual occasions that a reminder was triggered) and the proportion of these occasions that produced the target response. However, others reported outcomes in terms of the proportion of patients in the two arms having received a screening test, vaccination, prescription, etc at the end of the study period, without being able to provide information on the actual number of ‘point of care’ opportunities involved. In other words, the outcomes were based on population level data rather than those relating to individual consultations and their outcomes. During the study, a number of opportunities might have arisen for a clinician-patient encounter to be influenced by a

reminder in a consultation. If the number of such actual encounters were reported, this might provide the denominator most likely to produce comparable estimates of effect between studies, as the methodological diversity might be reduced significantly in this subgroup.

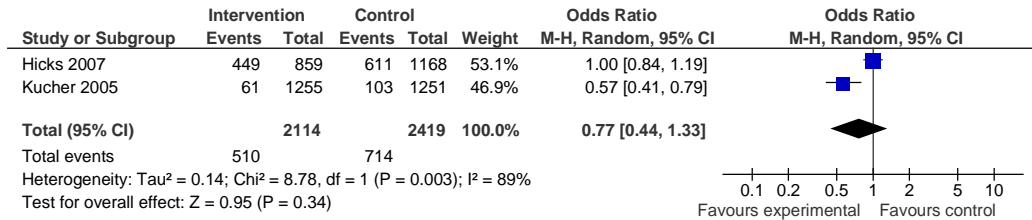


Figure 4.1: Forest plot of the two studies reporting a clinical outcome. In the case of Hicks 2007, the numerator has been adjusted to produce the same direction of effect as for Kucher 2005.

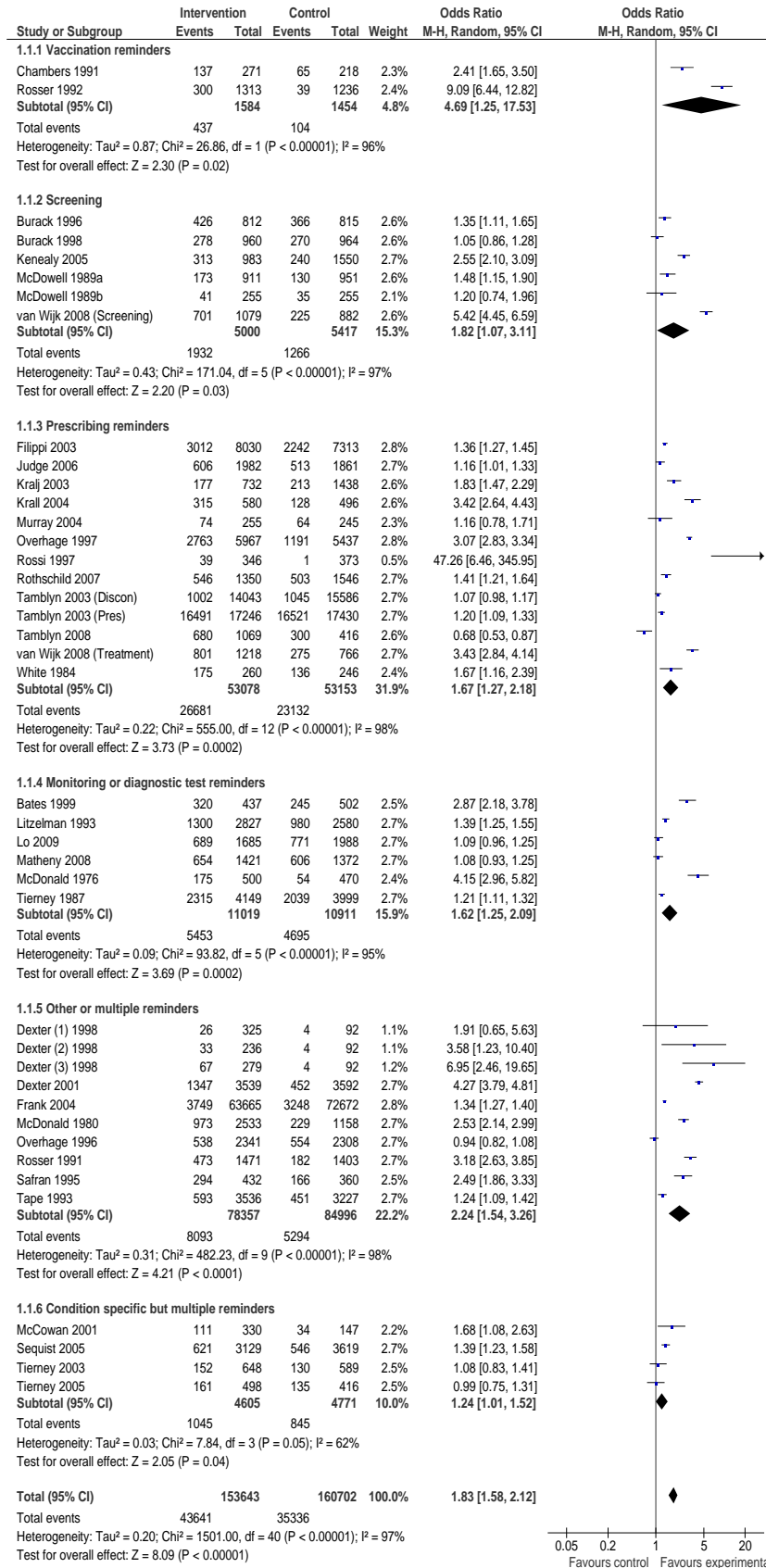


Figure 4.2: Forest plot of all studies reporting process outcomes, including either population or reminder opportunity denominator, grouped by area of care.

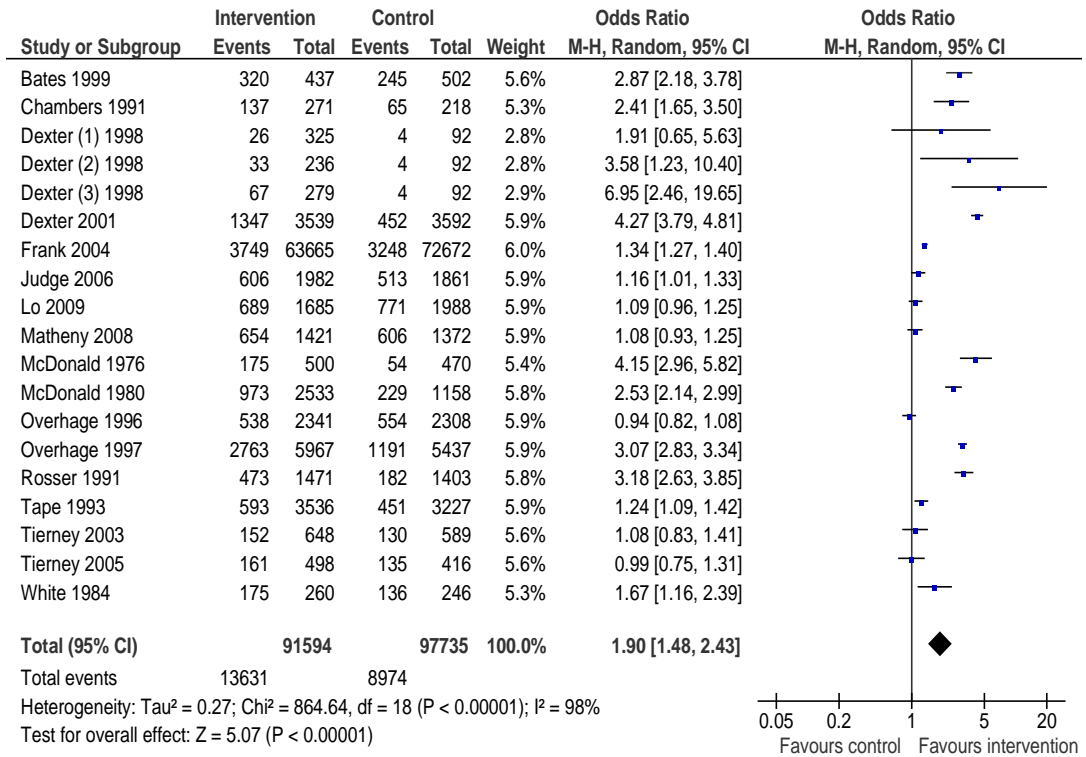


Figure 4.3: Forest plot of all studies using the reminder opportunity as the unit of analysis.

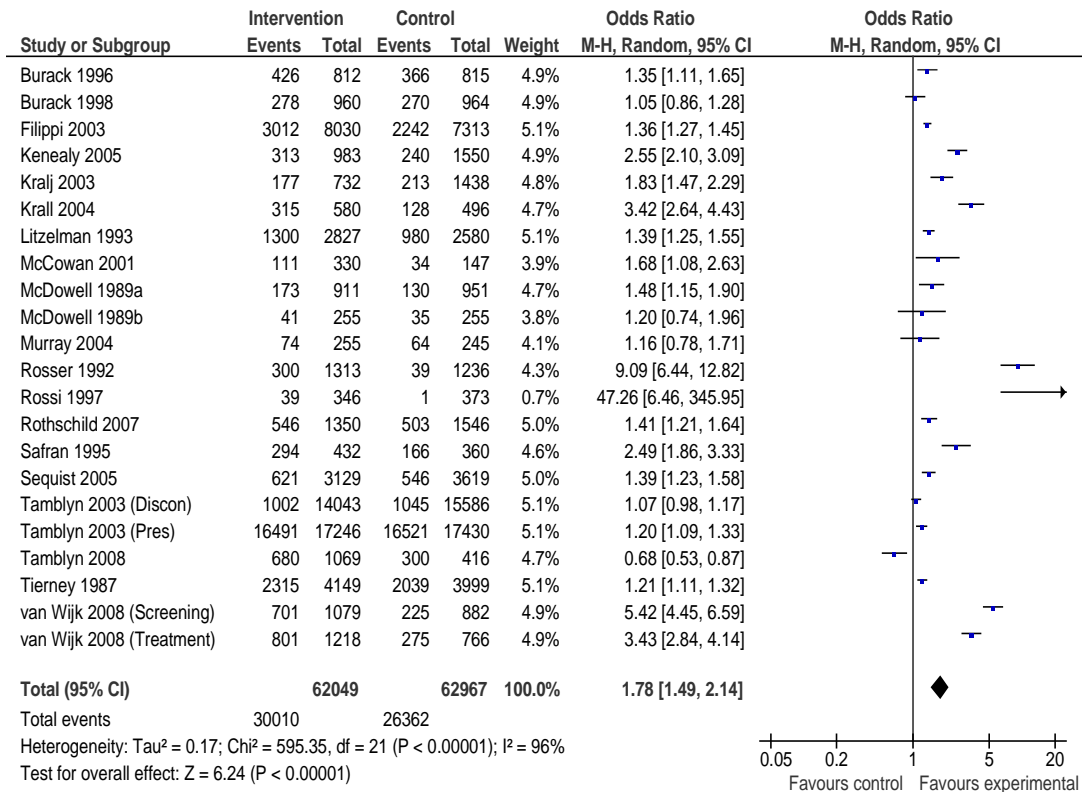


Figure 4.4: Forest plot of all studies using a population level denominator as the outcome.

This distinction was more difficult to make than expected. A number of studies reported 'Intention To Treat' outcomes in which the denominator included identifiable patients potentially eligible to trigger a reminder but who did not actually present to the practice to be exposed to the intervention. In other cases, only the patients actually presenting were analysed. Where both were available, we used the intention to treat data. However for some studies, presentation at the practice was an inclusion criterion for enrolment in the study as well as eligibility for a reminder message (e.g. Van Wijk 2008).

A further issue concerns the weighting of studies in which multiple reminders were used as part of a decision support system, and the numbers eligible for each reminder were reported at the start and the end of the trial. Through aggregation of the data provided (to derive an overall figure for the effect of the reminder system) there was a risk of double or multiple counting, as individual patients may justify more than one reminder. A related issue is whether a screen reminder listing more than one different care suggestion is delivering more than one reminder. If a practice identified 100 patients requiring influenza vaccination and 50 requiring pneumococcal vaccination, there might be 40 people requiring both. These 40 people would receive a reminder (about both issues at the same time) if they presented to the practice, but our extracted denominator would be 150, as the articles do not generally report the overlap between groups eligible for separate reminders. We applied the same policy consistently in the analysis, regarding each 'sub-reminder' as an intervention in itself. If a clinician responded to the combined reminder by arranging influenza but not pneumococcal vaccination, this would only 'count' as a response to one of two reminders.

#### **4.11.4 Results of the process outcome studies**

As discussed above, the majority of studies investigated the effects of reminders on processes of care. These were analysed separately in RevMan from the two clinical

outcome studies and the results are given in Figures 4.3 and 4.4, and Table 4.7. For the combination of all binary outcome process of care studies an overall Odds Ratio of 1.83 [95% CI 1.58, 2.12] was derived, indicating a significant but modest benefit of the intervention. One study (Shea 1995) reported a continuous outcome (length of hospital stay), and a non-significant change.

#### **4.11.5 Clinical outcome studies**

Two studies reporting clinical rather than process of care outcomes (Kucher 2005 and Hicks 2007) are considered separately. In the case of Kucher 2005, a positive effect on the rates of venous thromboembolism was detected through point of care reminders related to thrombosis risk in hospital inpatients. An odds ratio of 0.57 [95% CI 0.41, 0.79] for risk of clinically significant thrombosis, was derived.

I adjusted the numerator of the Hicks 2007 study as it would otherwise have suggested an effect in the opposite direction to Kucher 2005. I calculated the odds of *not* having blood pressure controlled (the adverse outcome that the intervention tries to prevent) rather than the odds of the blood pressure being controlled (as is reported in the paper). This makes the analysis comparable with the Kucher study, in which the odds of a thrombo-embolic event are similarly reduced (not increased) by the intervention. Hicks 2007 dilutes the effect of Kucher 2005 to give an overall non-significant odds ratio of 0.77 [0.44, 1.33] for the two clinical outcome studies.

#### **4.11.6 Comparability of studies**

My attempts to identify a subgroup with a low heterogeneity score were only partially successful. The areas of care categories that I identified all had high levels of heterogeneity, with one exception: the Condition specific reminder group. This group produced a Tau<sup>2</sup> score of just 0.03 and a Chi<sup>2</sup> test of borderline significance (p=0.05), in contrast to all the other groups, in which the p value for the Chi<sup>2</sup> was <0.00001 (Table 4.7). This p value is the probability that the null hypothesis of no heterogeneity

is true.  $\text{Tau}^2$  is the variance of the measured effect of the intervention between the included studies. Monitoring and diagnostic test reminders also seemed to be less heterogeneous than others, with a  $\text{Tau}^2$  of 0.09, but still produced a low p value for the  $\text{Chi}^2$  test.

By dividing the studies by unit of analysis I attempted to distinguish between the efficacy of the reminder intervention at the point of care from its effectiveness in altering population level outcomes, as discussed earlier. However the  $\text{Tau}^2$  measures obtained in these study subgroups were not significantly lower than those of the overall sample (Table 4.7).

Category	$\text{Chi}^2$ test for heterogeneity (p value)	$\text{Tau}^2$ measure of heterogeneity	Odds Ratio [95% CI]
<b>All process of care studies reporting binary outcomes</b>	1501.00 df=40 (p<0.00001)	0.20	<b>1.83</b> [1.58, 2.12]
Vaccination reminders	26.86 df=1 (p<0.00001)	0.87	4.69 [1.25, 17.53]
Screening reminders	171.04 df=5 (p<0.00001)	0.43	1.82 [1.07, 3.11]
Prescribing reminders	555.00 df=12 (p<0.00001)	0.22	1.67 [1.27, 2.18]
Monitoring or diagnostic test reminders	93.82 df=5 (p<0.00001)	0.09	1.62 [1.25, 2.09]
Other or multiple reminders	482.23 df=9 (p<0.00001)	0.31	2.24 [1.54, 3.26]
Condition specific reminders	7.84 df=3 (p=0.05)	0.03	1.24 [1.01, 1.52]
Unit of analysis = the reminder opportunity	864.64 df=18 (p<0.00001)	0.27	1.90 [1.48, 2.43]
Unit of analysis = population denominator	595.35 df=21 (p<0.00001)	0.17	1.78 [1.49, 2.14]
<b>Both clinical outcome studies</b>	8.78 df=1 (p=0.003)	0.14	0.77 [0.44, 1.33]

*Table 4.7: Heterogeneity values and odds ratios for all the binary outcome studies and for various subgroups of process outcome. The clinical outcome studies aim to demonstrate a reduction in events with an odds ratio less than unity.*

#### **4.11.7 Sensitivity analysis: exclusion of a study involving rare events**

Individual studies may produce very high odds ratio values simply because there are either no events, or very few events in the control arm. Rossi 1997 was such a study, with only one event recorded in the control arm, producing an outlying odds ratio of 47.26. A zero value for the numerator in the control arm would produce an effectively infinite odds ratio. In such cases, RevMan automatically inserts a value of 0.5 to the empty cell.

Such results are not particularly helpful in a quantitative analysis, but the use of reminders in settings where there is essentially no activity in the control situation is not unimportant. The high odds ratio value of Rossi 1997 does not contribute much to the overall result, as the weight of this study is low (0.5%). The value of the overall odds ratio was only slightly reduced (OR 1.81, CI 1.56 – 2.09) when it was excluded from the analysis.

#### **4.11.8 Other studies included in the review but not in the RevMan analysis**

Eccles 2002 was a study of a system of reminders to support the care of patients with asthma and angina. It reported many different outcome measures, and gave individual odds ratios for all of them, but no single measure was identified as primary. I contacted the lead author Martin Eccles for advice on the handling of this paper, which had been included in the Shojania 2009 review. He advised me that a technique had been developed by the Cochrane EPOC group for synthesising such results to derive a median effect size estimate for all the measures within the study. As the Shojania review used a different measure of effect size (based on percentage improvement in process adherence or clinical endpoint rather than an odds ratio) we decided not to include this study in our RevMan analysis. It was nevertheless accounted for in the



narrative synthesis as an example of a high quality, condition specific study reporting non-significant outcomes.

## **4.12 Influence of excluded papers**

A number of papers were identified that were not ultimately included in this review but that nevertheless influenced this thesis. Some of these were cited in the e-Nudge trial protocol as they influenced the design of the e-Nudge intervention and are mentioned in Section 1.5 of Chapter 1, and in Section 9.6 of Chapter 9.

In a 1992 paper, Clement McDonald (51) described a follow up investigation of the participants of a previous reminder intervention trial of 1984 (52). The original trial had measured the effect of reminders on multiple outcomes including vaccination rates. It was only excluded from our review because denominator data were not reported and attempts to obtain them from the lead author were unsuccessful. In the second study, the individuals originally allocated to receive vaccination reminders, and the controls, were followed up to determine morbidity outcomes (chest xrays, blood gas analysis, and hospitalisations). All three outcomes were lower in the patients originally allocated to the intervention arm of the 1984 study. Whilst this second study was not eligible for our review, the result suggests a significant potential impact of electronic reminders on clinical outcomes.

## **4.13 Conclusions**

Computer generated, patient specific reminders available at the point of care are generally beneficial, although the effect on clinician behaviour is not strong. For studies reporting process of care outcomes, we derived an overall odds ratio of 1.83 [95% CI 1.58 - 2.12]. This is comparable with the results of other, similar reviews discussed in Chapter 1. Clinical outcomes have been used much less often than process outcomes as the primary measure. However, the effect of reminders is inconsistent and

may depend on the organisational context. Trials reported in the published literature are heterogeneous in their designs, as well as in their operational environments, making evidence synthesis problematic. As the perceived importance of a reminder by the target clinician may determine its impact, and priorities differ among clinician groups, the effectiveness of a new intervention cannot easily be predicted. This perhaps accounts for the repeated trialling of apparently similar interventions throughout the last three decades.

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## **Chapter 5: The e-Nudge trial: preparatory pilot work**

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### **5.1 Introduction**

The e-Nudge trial resulted from the opportunities arising from my move to Warwick in 2004 and my new role as deputy director of Warwick West Midlands Primary Care Research (later Warwick-Coventry Primary Care Research). But the concept of applying a CVD risk algorithm to general practice data had already been developed in my previous post and in fact piloted as early as 1997. This chapter will describe how the background work prior to the trial facilitated its design and implementation.

### **5.2 Identifying potentially at risk groups**

General practice computers have, as described in Chapter 1 provided from the early 1990s a rich source of cardiovascular risk factor data, potentially providing new means of addressing cardiovascular risk (1). But such resources contain information that is different from that collected in more formal research settings (2), and inevitably include missing data points that need to be accounted for to maximise the accuracy of risk estimates and the usefulness of the data source. Through this research I was able to measure the proportion of the general practice population whose basic risk profiles were complete and this will be described in the results chapter. However I also found that such patients are out-numbered several fold by those requiring further information to estimate risk, raising practical issues.

One option to overcome the problem of missing information is to insert specific 'assumed' values, typically involving a single estimate for each factor applied to all those in whom these data points are missing. This approach may fail to recognise that those with missing data are not necessarily representative of the general population

from which the assumed values are derived, but is a pragmatic means of utilising the data that *are* present, and has become commonplace in the development of risk algorithms as described in Chapter 2. A group characterised by a certain (perhaps unknown) threshold of sensitivity and specificity for case recognition is then identified, depending on the set of chosen values for the missing risk factors. In the e-Nudge trial, these values were based on the median values from the Health Survey for England 2003 (described in the next chapter). This approach does not recognise adequately the range of potential values for these missing data and the impact this range might have on case finding. It also misses an opportunity to allow assumed values to be influenced by the other (known) risk factor values. Known correlations between risk factors represent a potentially useful means of optimising the estimation of ‘assumed’ values, and could be based on the relevant background population. This possibility was suggested in my original publication in this area (3), and has also been used by Marshall (4-6).

Another approach is to recognise the limitations of the data source and to target subgroups of the population not for treatment on the basis of assumed values, but for clarification of risk through the systematic gathering of complete risk profiles. This was the original basis for the advice given in the National Service Framework for Coronary Heart Disease (2000) (7), which recommended that patients on the general practice diabetes and hypertension registers should be targeted first for risk assessment (i.e. before the rest of the practice population). This was advised irrespective of the existing risk factor data held on individual patients (other than their diagnoses of diabetes or hypertension), except that older patients would clearly be more likely to produce a greater yield of high risk cases than younger patients within these groups.

More recently, the same concept has become the basis for the 2008 NICE guidelines on Lipid modification CG67 (8), which recommends the targeting of groups for cardiovascular risk reduction using primary care data. These two guidelines (separated by eight years) both advocate that groups *potentially* at risk (on the basis of existing, routinely collected data that are likely to be incomplete in most cases) should

be identified initially, and then invited for more accurate clarification of risk through completion of a more personalised risk profile, including data that may not be electronically recorded, such as ethnicity, family history, obesity, and social deprivation. This issue became important to an ongoing debate over the relative merits of the QRISK algorithm and the longer established Framingham algorithm as applied to UK primary care data. General practice data have improved significantly in quality and completeness since a decade ago, but are still considered inadequate as a basis for a definitive recommendation over the need for lipid lowering therapy in the case of an individual whose CVD risk had been identified purely on the basis of routinely collected primary care data.

I had explored this area in an early practice based project carried out at in Danby, North Yorkshire in 1997 that was subsequently published in a book chapter (9). This project was carried out before I registered for the PhD (and is therefore given in the Appendix as it is separate from the thesis material) but provides useful background. It used the Sheffield tables (10) to construct a series of searches in EMIS LV defined by the tables' individual 'cells.' These tables were at the time the most readily available means of identifying potentially 'at risk' groups requiring cholesterol measurement, and were (like most other commonly used approaches of that time) based on Framingham study data. The first published application of a risk algorithm applied specifically to UK general practice data (11) involved the Sheffield tables. The focus of the Sheffield table authors was on the targeting of individuals for cholesterol measurement, rather than on the identification of established cardiovascular risk. In other words, it aimed to identify groups requiring further assessment of risk, rather than those whose risk was already demonstrated by the data.

The approach used in this survey was an extremely pragmatic one: rather than attempting to complete the cardiovascular risk profiles of the entire population, individuals were only identified if they had a reasonable chance (based on existing, usually incomplete data) of producing a high CVD risk estimate. This approach would

support the current recommendation that primary care should host the identification of candidates for risk estimation. An alternative approach in which all potential candidates for risk reduction (e.g. the entire 40-74 year age group) were invited for formal risk assessment irrespective of their (already established) risk factors would not need the support of primary care data and could be undertaken in alternative (e.g. non-NHS) settings.

But the conclusion of this pilot work was that despite incomplete data, groups may be recognised on the basis of just a few risk factors that are likely to have a much higher yield of cases of raised CVD risk than would be possible using approaches independent of primary care data.

An equally important suggestion was that targeting might involve a *two stage* process: an initial stage identifying a potentially at-risk group and the second stage more accurately quantifying individualised risk by incorporating information that was only partially represented by electronic data. This thesis attempts to inform both stages of this process, and to comment on the adequacy of routinely collected primary care data to support them.

### **5.3 The Newchurch experience**

After moving to the University of Warwick to commence the PhD I began discussions with the private software company Newchurch (now Tribal Newchurch). This is an independent company managing NHS data that provided an integrated system of data capture and storage for 26 South Warwickshire practices following a ‘Demonstrator’ project completed in 2003 (12). All Read coded data were extracted every 24 hours and made available to selected NHS professionals in the locality. These included Accident and Emergency departmental staff, who were able to access data on limited past medical history, medication, allergies and electrocardiographic records to assist with the immediate care of patients presenting in the department. When I began in my

current post in South Warwickshire in 2004 as an academic interested in NHS data integration (and as a GP working in a practice connected with the Newchurch database) I was interested to know more about this development. In addition to the experience of local stakeholders involved in the establishment of this system (who had undergone an extensive process of negotiation with public and professional bodies over data control and Caldicott issues) I was also interested in the future potential of the system to provide the functionality I envisaged for the support of systematic cardiovascular risk reduction in primary care. Five meetings took place between 18.4.05 and 27.1.06 at their Teddington, London headquarters, where this database was hosted.

The first meeting with the company's Junaid Khan involved an exploration of the possibilities offered by the Newchurch database, and its potential to support the e-Nudge trial. Further meetings involved an in-depth study of the data extracted from my own practice (Castle Medical Centre, Kenilworth) by Newchurch that, along with all the other practices, were updated every 24 hours. Permission was gained to proceed with this from my partners and practice managers. The most interesting and relevant work involved the construction of the Framingham equation as a search algorithm by Newchurch's Muhmud Ahmad, with whom I spent several hours at each meeting examining remotely my own practice's data via the NHS Net. This work preceded the subsequent publication (using a similar technique) by Marshall (5), and the more recent QRISK studies that used the same approach on a much larger scale (13, 14). It represented a significant advance on the previous Sheffield audit carried out in Danby in 1997. Instead of identifying groups justifying cholesterol measurement, it identified groups whose existing data were sufficiently complete to suggest raised cardiovascular risk. More importantly for my purposes at the time, it enabled me to experiment with alternative values of the missing variables, to measure the impact that a range of assumptions would have on the numbers identified. Some of the results of this work are given in Tables 5.1 and 5.2 and the Box).

Applied	14
Deceased	1250
Permanent	10709
Temporary residents	18
Transferred out	15715
Undefined	1702
<b>Effective active practice population:</b>	<b>12,425 (Applied+Permanent+Undefined)</b>

Table 5.1: Castle Medical Centre list size on 10.1.06

Search number	Assumed systolic BP if absent or out of date	Assumed total serum cholesterol if absent or out of date	Assumed serum HDL cholesterol if absent or out of date	Assumed smoking status if absent	Assumed diabetes status if no recent blood glucose	Number identified
1	143 (male) or 142 (female)	5.8 (male) or 6.25 (female)	1.2 (male) or 1.5 (female)	Non-smoker	Positive	2578
2	143 (male) or 142 (female)	5.8 (male) or 6.25 (female)	1.2 (male) or 1.5 (female)	Non-smoker	Negative	1554
3	143 (male) or 142 (female)	5.8 (male) or 6.25 (female)	1.2 (male) or 1.5 (female)	Smoker	Positive	2878
4	143 (male) or 142 (female)	5.8 (male) or 6.25 (female)	1.2 (male) or 1.5 (female)	Smoker	Negative	2085

Table 5.2: Experimenting with my own Kenilworth practice's (anonymised) data remotely from Newchurch's Teddington data warehouse on 10.1.06. The aim was to tune the assumed values to produce a manageable population size likely to benefit from further data collection. The assumed values later used in the e-Nudge software were based on the more recent Health Survey for England 2003 (15).

However, the derivation of these results brought up immediate problems with data quality that took some time to investigate and proved impossible to overcome within the Newchurch system. My ability to follow up individual examples of patients with irregularities (identified at Newchurch through their EMIS computer number) back at the practice in Kenilworth facilitated this process. For instance, patients were identified with no apparent record of cardiovascular disease but who appeared in the searches as

if such a record were present. A practice based audit trail was necessary to explain this anomaly. Such patients had been diagnosed (perhaps provisionally) with some form of CVD whilst our clinical software system was EMIS GV, the system used until 2002. During that year the practice changed from EMIS GV to EMIS PCS, and the electronic records were transferred to the new system through a data migration process. During this process any previous codes that were considered irrelevant (such as unconfirmed CVD) were lost from the clinical notes but were still detectable in the Newchurch searches. This finding could be assumed to apply to all of the practices connected to Newchurch, and clearly threatened the ability of this system to support the trial, particularly as such examples were not uncommon.

A further, equally important problem that became evident was that Newchurch practices were not generally using their system to any extent in everyday practice, with a few exceptions. Each connected practice (including my own) had a Newchurch server installed that could be accessed from consulting room computers, and a wide range of information was available including practice based demographic and morbidity patterns. However, the usage of this resource appeared to be low. This was evident not only through visiting and contacting Newchurch practices, but also through actually asking Newchurch to provide data on system usage through 'logging in' reports. As discussed in the paper I co-authored with Ian Allwood (12), it emerged that the main role for Newchurch in the area was to provide access to patients' records by out of hours providers including the Warwick Hospital Accident and Emergency Department. This was an important and valuable resource, but unless the search results on cardiovascular risk patterns could be fed back to clinicians during routine primary care, the e-Nudge trial could not be supported. This experience provided an important lesson that had been relevant to the literature review of this thesis, over the availability of 'feedback' information *within the consultation environment*, without which electronic reminder interventions are less likely to influence the behaviour of health professionals.

## **5.4 Original links with Egton Medical Information Systems**

### **(EMIS)**

Before moving to the University of Warwick I had established connections with Egton Medical Information Systems (EMIS) partly through the geographical proximity of my former practice with the nearby Egton practice where the company was established, but also more specifically because of opportunities I used to share ideas with the company over the use of general practice data to target patients for cardiovascular prevention. After I moved to Warwick, EMIS were willing to support the research that resulted in the e-Nudge trial and, when it became apparent that Newchurch could not provide a sufficient platform, EMIS's Medical Director David Stables agreed to provide the necessary technology and expertise.

Collaborative work with EMIS began during late 2005, and the e-Nudge algorithm was programmed early in the following year. The Framingham equation coefficients from Anderson et al 1991 (16) were programmed in SQL to run on their LV system and adapted to receive primary care data as inputs to the algorithm. The SQL program is given in the Appendix.

## **5.5 Developing links with local health care organisations**

Preparing for the trial also brought me closer to South Warwickshire Primary Care Trust, their Head of Information Technology David Harry who was Newchurch's main contact, their information technology lead and Stratford GP Dr Ian Allwood, and their director of Public Health Dr Stephen Munday. All three had been actively involved with the Newchurch 'Demonstrator' project that had established this local resource. In addition, I began working closely with their front line IT technicians Paul Elwell and Olly Scholefield, who were actively involved in administering IT solutions and conducting audit work throughout the practices of South Warwickshire. At a PCT meeting with Olly Scholefield in 2005 I was introduced to Juelene White, Service



Improvement Manager for the South Warwickshire (and subsequently Warwickshire) PCT who recruited me to join the Trust's Coronary Heart Disease National Service Framework Local Implementation Group, and later their Long Term Conditions Group. This helped me ensure that my research remained aligned with the priorities of service based as well as academic primary care. Through my University role I also sat on the Research Strategy Board of South Warwickshire PCT (Research Management and Governance), its Research Steering Group, and (following the merger of local PCTs and the creation of the National Institute for Health Research's Primary Care Research Network), the PCRN (Central England)'s Executive Board.

## **5.6 Funding for the trial**

The e-Nudge project was funded by a PhD studentship from Warwick Medical School which in 2005 benefitted from money distributed by the Department of Health to the newer UK medical schools. A grant of £104,304 was obtained to study the use of primary care data to support cardiovascular risk estimation. Whilst the application process was peer reviewed this was carried out on an internal or local basis, and the trial did not therefore qualify for later inclusion in the UKCRN portfolio. Such inclusion might have benefitted the trial in its later stages (through access to service support payments) but did not hold it back in any other way, as the recruitment of trial practices and the instalment of the e-Nudge algorithm did not require such support.

## **5.7 Ethical and R&D approval**

Ethics approval for the e-Nudge trial was gained from Warwickshire Local Research Ethics Committee in August 2005. By this time I had successfully engaged Newchurch and EMIS but it was still not clear which of the two would actually provide the platform for the trial. One ethical issue that required consideration was the ability of Newchurch to process the data using the Framingham algorithm to identify at risk

patients (a process that would have to take place in Teddington), and to then transmit results back to the practices, without breach of confidentiality. Permission was gained for this on the basis that Newchurch were contracted by the NHS, bound by its Caldicott regulations, and connected to practices via the NHSNet, but in the end only EMIS were able to provide a platform for the searches that identified individuals without any information leaving the practice, a more satisfactory arrangement. The results of these searches could in principle be accessed remotely by EMIS (which facilitated numerous de-bugging and trouble-shooting exercises following e-Nudge installation) but the searches actually took place in the practices following the installation of the software to each participating practice's main server.

NHS Research and Development (R&D) permission was gained initially from South Warwickshire Primary Care Trust (PCT). This PCT was the Research, Management and Governance PCT for the West Midlands South Consortium of PCTs, which at the time included Coventry, Rugby, and North Warwickshire PCTs. After EMIS took over from Newchurch as the platform provider for the trial, the number of practices able to take part increased dramatically.

## **5.8 ISRCTN Registration**

I registered the trial with ISRCTN on 15 March 2006 This registration facilitated the publication of the trial protocol in April 2006 (17).

## **5.9 Peer review**

Feedback on the design of the trial was obtained from:

- **Peer review of the successful PhD Studentship obtained from Warwick Medical School in 2005.** Initial feedback questioned whether the project was feasible within budget but was otherwise very positive and the PhD was funded.

- **Professor Sallie Lamb and Dr Simon Gates of the Warwick Clinical Trials Unit.**

Their written feedback guided the subsequent implementation of the trial.

- **Dr Sandra Eldridge of Queen Mary University of London**, who advised on statistical issues arising from an earlier draft of the trial protocol.

- **The School of Health and Related Research (ScHARR) in Sheffield.** I was invited to give a seminar on 6/3/06 at ScHARR in which I discussed the design of the trial and the potential for primary care data to provide the basis for more complex, adaptive algorithms for recognising cardiovascular risk through data mining techniques. Useful feedback was obtained over the implementation of the trial even though it was too late at this stage to influence its design.

- **A visit funded by Warwick Medical School to Montreal and New Brunswick in October 2006**, through which I presented the design of the trial to colleagues at McGill University and to the University of Moncton, where my colleague Sylvie Robichaud-Ekstrand is now based. Sylvie had previously worked at McGill with Robyn Tamblyn, who hosted the McGill meeting, and whose work on the ‘Medical Office of the Twenty-first Century (MOXXI)’ was to feature in the subsequent literature review.

- **The Randomised Controlled Trials course, Oxford University, April 2006.** Whilst it was by this time too late to change the trial protocol, valuable lessons were learnt particularly relating to the issue of Intention To Treat that were later to become important in the analysis of the results.

## **5.10 Summary**

The preparatory work described above was important for formulating the ideas and hypotheses to support the design of a randomised controlled trial of a (fairly) complex intervention. A particularly significant ‘thread’ emerged through this process: the distinction between identifying potentially at risk individuals and the clarification of risk status through more formal assessment. This distinction originated through the

Sheffield project work (prior to commencing the PhD), was developed during the PhD through collaborations with Newchurch, and later became the basis for the e-Nudge software programmed by EMIS as a 'case finding' tool rather than a definitive risk calculator. The design of e-Nudge, specifically for the purposes of a randomised controlled trial in primary care is discussed in the next chapter.

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## Chapter 6: Detailed methods for the e-Nudge trial

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### 6.1 Introduction

The aim of this research was to investigate the use of primary care data to support targeted cardiovascular risk reduction. The more specific objective of the e-Nudge trial was to test the effect of electronic reminders designed for the same purpose in the routine general practice environment. Some of the methodological details discussed here are adapted from the e-Nudge study protocol published in the journal *Trials* (1), and others from the final trial report (2). The first of these publications (describing the design and methods) was aligned where possible with the revised CONSORT statement of 2001 (3). The final report was also guided by a more recent extension of the statement specifically for pragmatic trials published in November 2008 (4).

### 6.2 Outline of the e-Nudge trial design

#### 6.2.1 Hypotheses

I hypothesised that an automated system of electronic reminders drawing on routinely collected primary care data would improve the visibility of the population at risk of cardiovascular disease (CVD), the adequacy of cardiovascular risk factor data, and ultimately cardiovascular event rates.

#### 6.2.2 Setting

The trial was set in the routine environment of primary care in the United Kingdom (UK).

### **6.2.3 Participants**

The over 50 year old population registered with 19 general practices in the West Midlands of the UK.

### **6.2.4 Intervention**

The 'e-Nudge' software tool was designed to extract data from practice systems and generate regularly updated lists of patients in six groups. These were based on estimated risk of cardiovascular disease, adequacy of data to support risk estimation, the need for clarification of diabetes status, and persistently raised blood pressure in patients over 75 years. Intervention patients currently identified in any of the lists received a screen reminder whenever their electronic record was accessed. Practice teams could examine the lists of identified patients if they wished and were reminded about them every eight weeks by an email sent to a nominated team member. Responses to the notification mechanisms (lists and screen reminders) were entirely optional.

### **6.2.5 Control condition**

The control arm would receive usual care without the assistance of e-Nudge software, but practitioners would employ their usual means of assessing cardiovascular risk, including the use of currently available software tools. The use of such tools in UK practice during the trial was not very commonplace. All practitioners involved in the trial were in receipt of the British National Formulary (updated every six months), which contains risk charts recommended by the Joint British Societies for calculating cardiovascular risk.

### **6.2.6 Outcomes**

1. Annual rate of cardiovascular events in the over 50 year population.

2. Proportion of the trial population identified in each of the e-Nudge Groups at the end of the study. The mean of the proportions in the final three eight-weekly data captures would be used to define this outcome.

### **6.2.7 Duration of the study**

Twenty-four months.

### **6.2.8 Analysis**

By intention to treat, using Poisson inference techniques for cardiovascular event rates (primary outcome), and Chi-squared tests for Group differences (secondary outcomes).

### **6.2.9 Quality assurance**

A sub-study of the trial population was used to confirm the validity of the primary outcome search techniques.

## **6.3 The e-Nudge algorithm**

The e-Nudge algorithm was only part of the e-Nudge intervention. A flow diagram defining the e-Nudge Groups 1-6 is given in Figure 1. The code sets were wherever possible the same as for the quality and outcomes framework (QOF). The inputs were based on the most recent values of the risk variables (or in the case of systolic blood pressure, an average of up to three recent values). I chose this option over alternatives (e.g. pre-treatment levels, where available, or highest ever level) for two main reasons. First of all, there was an increasing move to base risk estimates on current data rather than 'pre-treatment' data, recognising that for many patients it will not be clear enough which category an electronically retrieved measurement fits. In principle it is possible for a general practice computer to identify the date of onset of anti-hypertensive or lipid lowering drug therapy within that practice, but the patient might have already been



taking such therapy when registering with the practice. In other cases, the pre-treatment levels may pre-date the establishment of electronic records, making retrieval of the original levels impossible. This is an example of compromise (as both JBS2 and the later NICE CG67 stated a preference for pre-treatment values if available) due to the limitations of the source data. Its main implication was that a patient currently on treatment for either blood pressure or cholesterol might have their true risk underestimated by e-Nudge. For this reason, I was careful to emphasise to e-Nudge users that the software was a case-finding tool, not a definitive risk scoring algorithm. Estimated risk should be confirmed by practitioners if they considered it necessary. This might also include the use of other factors not included in Framingham but recommended in JBS2 for correcting the estimate. These factors include male Asian ethnicity, family history of CHD, impaired glucose regulation, hypertriglyceridaemia, low physical activity, and impaired renal function. The e-Nudge would be unlikely to actually overestimate risk, as most corrective factors inflate rather than reduce the initial estimate, and this was one of its strengths. A patient identified as at high risk would be unlikely to have a risk estimate less than 20% following the inclusion of corrective factors, and the use of most recent blood pressure and cholesterol data made this even less likely if these values were taken on treatment.

The second reason for using most recent levels as a basis for risk estimation was related to the trial design itself. The impact of the e-Nudge reminders on the Group proportions would be evident through the trial by determining the change in estimated risk based on these most recently recorded data. Action taken on the basis of a reminder (e.g. measurement of blood pressure in a patient requiring this to complete the risk profile, or correction of raised blood pressure by drug therapy) would only be evident if the most recent measurements were used.

A related issue is the existence of patients with diagnoses that have later resolved. The only disease diagnoses relevant to e-Nudge were those of ischaemic heart disease, cerebrovascular disease, and diabetes. In the first two cases, a patient is always

considered to be eligible for indefinite follow up if the diagnosis is confirmed and will remain on the register. This also applies to most cases of diabetes, but there are occasions when diabetes may arise temporarily (e.g. during high dose corticosteroid use) and later be considered to have resolved. The QOF recognises a code for ‘Diabetes resolved’ and this is included in the definition of QOF Diabetes disease registers. The e-Nudge was therefore able to incorporate this as well as it drew on QOF registers for this and the vascular diagnoses.

### 6.3.1 Framingham algorithm

The Framingham CVD algorithm as defined by Anderson et al (5) was used to identify patients for Groups 2 and 3 (later termed B and A). It has the following structure:

$$\mu = \sum \beta_i x_i$$

$$\sigma = \exp(\theta_0 + \theta_1 \mu)$$

$$u = (\ln(t) - \mu) / \sigma$$

$$p = 1 - \exp(-\exp(u))$$

where

$\beta_i$	=	the coefficient for each risk variable $x_i$
$x_i$	=	the value of the corresponding risk variable
$\theta_0$ and $\theta_1$	=	constants
$e$	=	the base of the natural logarithm
$t$	=	timescale for the risk estimate (10 years for this trial)
$p$	=	the probability of a cardiovascular event within this timescale

The values of the constants ( $\theta_0$  and  $\theta_1$ ) and coefficients ( $\beta_i$ ) for this equation are given in the SQL program in the Appendix. These coefficients are for the **CVD algorithm**

(not CHD, Acute MI, CHD death, stroke, or CVD death functions, which have different coefficient values). The risk threshold used to identify patients in this study is  $\geq 20\%$  in 10 years, which was the threshold recommended by the BHS Guidelines (6) and the JBS2 report (7).

### **6.3.2 Groups identified by e-Nudge**

Six groups 1-6 (later just four, relabelled A-D) were identified automatically using patient data and were updated every 24 hours to take account of new information. The search protocol is described in Figures 6.1-6.3. The original six groups can be summarised as:

**Group 1:** Patients over 50 years with existing cardiovascular disease or diabetes, whose blood pressure or cholesterol level is outside the Quality and Outcomes Framework (QOF) target range at the last estimation, or no “in date” level is recorded.

**Group 2:** Patients who are not known to have cardiovascular disease or diabetes, are *under 75* yrs old, and whose risk profile is incomplete – more information is required to perform a risk estimate - but whose cardiovascular risk would be greater than 20% if the “assumed” values of the missing factors were used (see below for definitions).

**Group 3:** Patients who are not known to have cardiovascular disease or diabetes, are *under 75* yrs old, and whose most recent Framingham variable values indicate that their risk level is raised.

**Group 4:** Patients who are not known to have cardiovascular disease or diabetes, are *greater than 75* yrs old and who have persistently elevated blood pressure based on the three most recent consecutive readings.

**Group 5:** Patients with possible undiagnosed diabetes, on the basis of at least one previous high blood glucose record (see below for more detailed definition).

**Group 6:** Patients with CVD but not diabetes, who have not had a blood glucose measurement in the past three years.

### 6.3.3 Definitions

**"In date"** means:

- A blood pressure reading within the last fifteen months for patients who have CHD/stroke/TIA or diabetes, otherwise three years.
- A blood glucose level within the last three years (for those without diabetes).
- A cholesterol level in the last fifteen months for CHD, Stroke/TIA or Diabetes patients, and three years for non-CHD/Stroke/TIA, non-Diabetes patients (applies to possible Group 2 patients).

**"Framingham variable"** means:

- Age
- Sex
- Smoking status (considered positive if record of smoking tobacco at last use of this Read code group, however long ago). A previously recorded smoker who has stopped will be considered a non-smoker only if 1 year has elapsed since quitting. A smoker is anyone who has smoked tobacco regularly in the past 1 year.
- Systolic blood pressure – average of last three "in date" values if available. If there are fewer measurements available, then the average of these is taken.
- Total serum cholesterol at most recent measurement, if "in date"
- Serum HDL cholesterol – as for total cholesterol
- Left Ventricular Hypertrophy status – assume negative unless there is any positive electronic record of LVH.
- Diabetes status, according to whether or not the patient is on the Diabetes register. However, if a primary prevention patient less than 75 yrs does not have a diagnosis of diabetes, but there is no blood glucose level "in date" (i.e. in the past three years), then

the risk algorithm will base the risk calculation on an assumption of positive diabetes status, and if the risk level is then high, the practice will be notified with this assumption stated, as a Group 2 message. If a patient (this time including those above 75 yrs) is not on the Diabetes register but there is a record of a blood glucose level  $\geq 11.1$  mmol/L, then the practices will be notified for clarification, regardless of the patient's CHD/Stroke status or calculated risk level, as a Group 5 patient. The matter can be clarified by the practice teams if they wish, by organising a fasting blood glucose (FBG) or oral glucose tolerance test (OGTT). A FBG  $\leq 6.9$  mmol/L or OGTT code following (at a later date to) the high random blood glucose level would mean that the patient is no longer in Group 5 (but may re-enter it if further raised blood glucose levels occur). The FBG or OGTT must be clearly recorded electronically by the practices using appropriate codes (to distinguish fasting values from random blood glucose values), or the patient will continue to be flagged up in subsequent searches. If, despite a normal FBG result or OGTT, a further raised random value subsequently occurs ( $\geq 11.1$  mmol/L) then once again the e-Nudge will question whether or not the patient has diabetes by including them in Group 5, until a further FBG  $\leq 6.9$  or OGTT code is recorded, or the patient is diagnosed and added to the Diabetes register.

**"Assumed values"** for the missing variables means:

For systolic blood pressure: Male 135 mmHg, Female 132 mmHg

For total serum cholesterol: Male 5.7 mmol/L, Female 6.2 mmol/L

For HDL cholesterol: Male 1.4 mmol/L, Female 1.7 mmol/L

For diabetes status: positive.

For smoking status: non-smoker.

The blood pressure and cholesterol thresholds are the approximate median or mean values in the 50–74 year age group taken from the Health Survey for England 2003 (8).

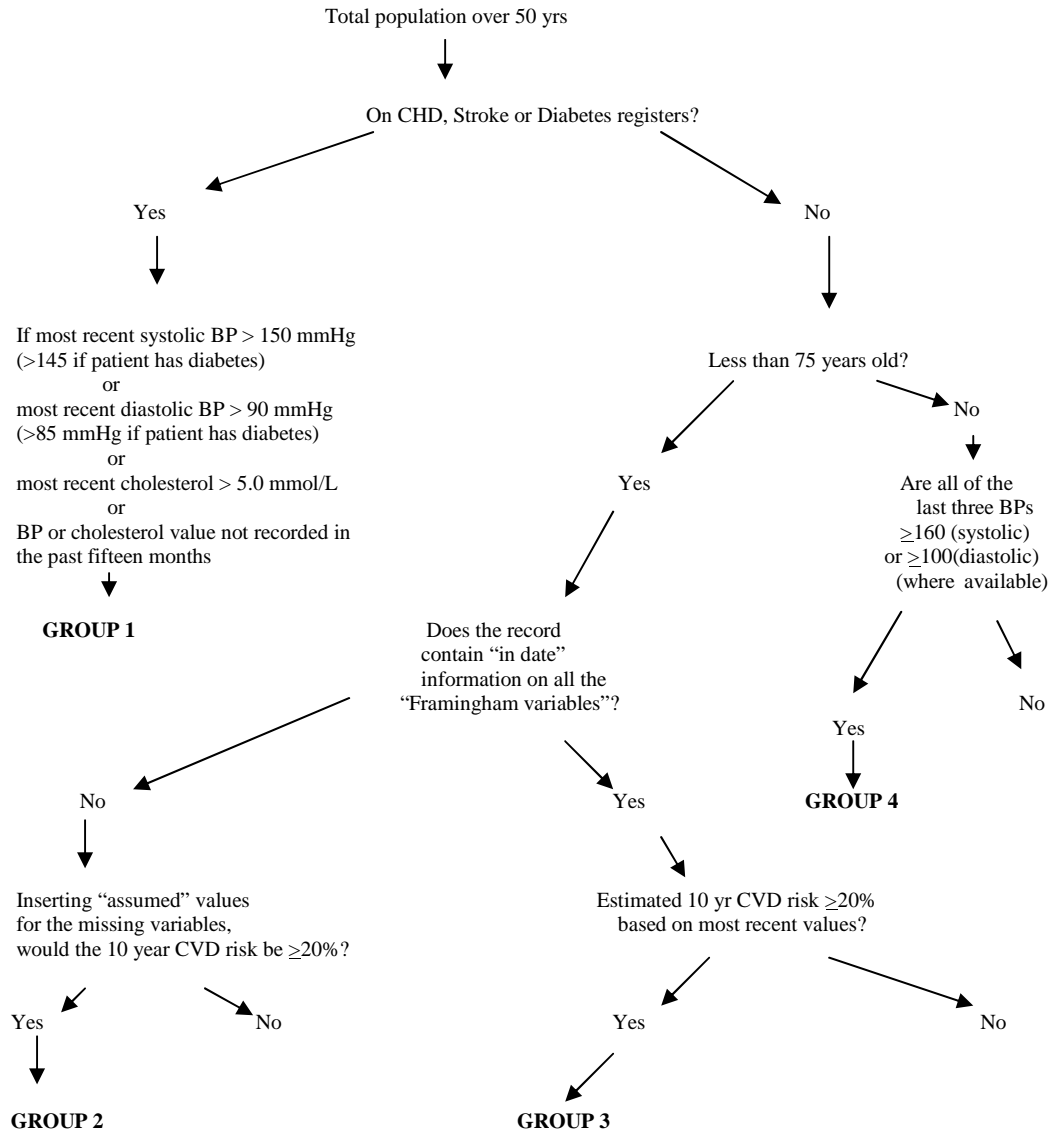


Figure 6.1: Identification of Groups 1-4.

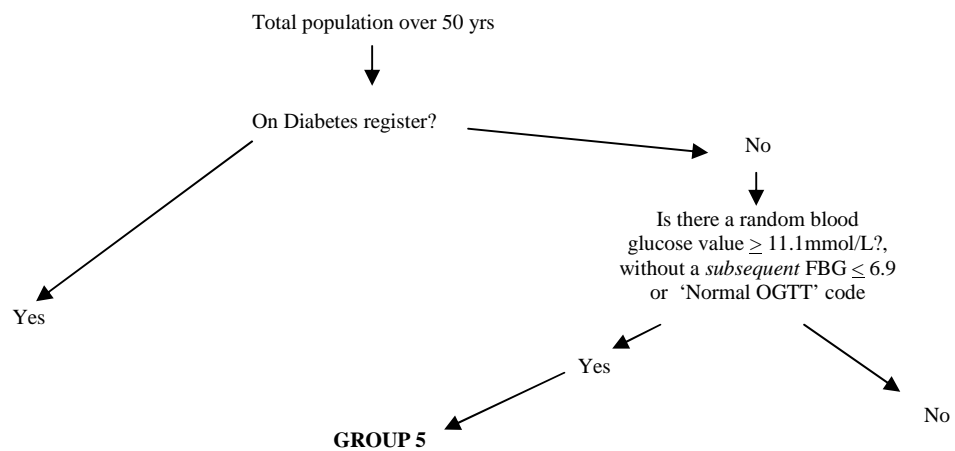
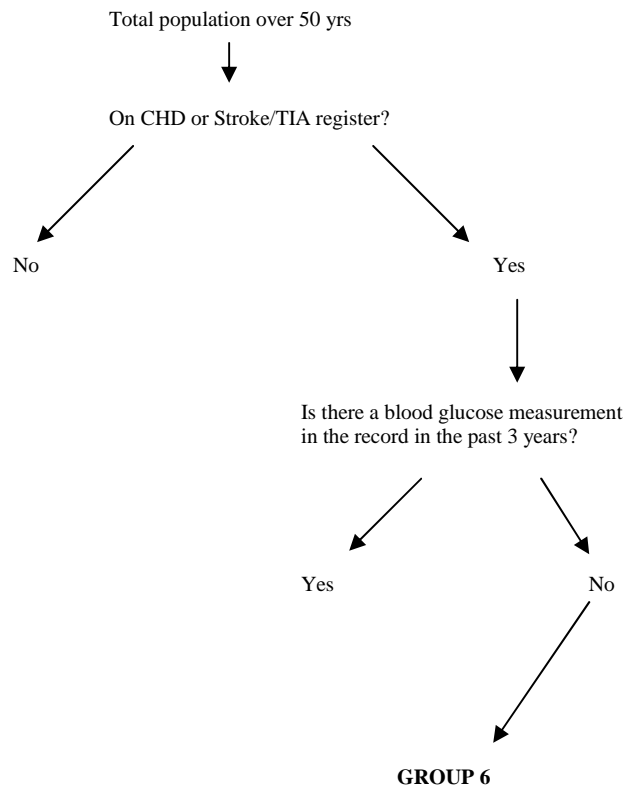


Figure 6.2: Identification of Group 5.



*Figure 6.3: Identification of Group 6*

The combination of groups 5 and 6 are those with ‘undefined diabetes status.’

#### **6.3.4 Changes to Group labels**

Groups 1 and 5 were later withdrawn for reasons discussed in Chapter 8, and the Group labels in the final report were altered as follows:

Group 2 became Group B

Group 3 became Group A

Group 4 became Group D

Group 6 became Group C

These changes were made also to emphasise the main focus of the trial, that was related to the primary prevention population at identifiable risk of CVD (Group 3/A).

## 6.4 The “e-Nudge” Intervention

### 6.4.1 Screen reminders and lists

Following the installation of the e-Nudge software to each practice’s database, searches occurred every 24 hours, and an automated system of reminders was created. Practice teams had the following notifications for intervention patients identified in the searches.

- **An eight-weekly email** was sent by me (based at the University of Warwick) to a nominated member of the practice reminding them of the availability of the e-Nudge lists stored in their system and accessible for the intervention patients.
- **Reminder messages** were displayed automatically on the computer screen each time an identified patient’s electronic notes were opened. Messages take two alternative forms in EMIS LV (for all types of reminder, not just e-Nudge): those appearing in the bottom right hand corner of the screen, and those appearing centrally. For practices using the corner message format, the message remains visible for the entire consultation unless the practitioner actively minimises it. This requires a mouse click on the screen message balloon. For those using the central screen format, a single ‘Return’ key stroke (*or* a mouse click on the message balloon) removes the message permanently from the screen for the rest of the consultation (although if a practitioner wished to be reminded of its message s/he could press keys Ctrl+F5 and it would appear again).

The messages contained the following wording:



**Group 1 reminder:** *The same as the existing QOF wording, as such patients represent an ‘out of QOF target’ group for risk factor control.*

**Group 2 reminder (later Group B):**

*This patient may be at high cardiovascular risk, but values for the following risk variables are either missing or out of date:*

**Missing variables:** *(Only lists those that are missing)*

*No recent systolic blood pressure value  
No smoking status recorded  
No recent total cholesterol value  
No recent HDL value  
Diabetes status needs clarifying*

*Note: Diabetes status is considered a missing variable if there is no blood glucose value recorded in the past three years, AND diabetes would put the patient in the high-risk category if positive)*

**Group 3 reminder (later Group A):**

*This patient’s estimated cardiovascular risk may be elevated, based on the most recent risk variable values.*

**Assumptions** *(For this group all are listed)*

*Average of recent systolic blood pressures:  
Smoking status:  
Most recent total cholesterol value:  
Most recent HDL value:*

**Group 4 reminder (later Group D):**

*This patient’s blood pressure is persistently elevated based on three consecutive values.*

**Group 5 reminder:**

*This patient **may have undiagnosed diabetes** based on a previous raised blood glucose level  $\geq 11.1$  mmol/L.*

**Group 6 reminder (later Group C):**

*This CHD/Stroke patient (states which) has no recorded blood glucose measurement in the past three years.*

**6.4.2 Amendments made to the wording of the e-Nudge alert messages**

Fairly early feedback from practices indicated that the screen messages needed shortening. This was particularly a problem for practices using the ‘corner alert’ format appearing at the bottom right hand side of the screen, as opposed to those using the centrally placed message format. This issue is discussed in Chapter 8. The messages were reduced in length (but to contain the same information) with agreement of Warwickshire Local Research Ethics committee, approximately nine months into the trial. The new wording was as follows:

**New Group 2 message:**

Possible CVD risk. Information needed:

**Missing variables:**

Blood pressure  
Smoking status  
Total cholesterol  
HDL cholesterol  
Glucose

**New Group 3 message:**

CVD risk may be elevated, based on:

**Assumptions**

Average of recent systolic blood pressures:  
Smoking status:  
Most recent total cholesterol:  
Most recent HDL:

**New Group 4 message:**

Persistently raised blood pressure

**New Group 6 message:**

CVD but no glucose recorded in past three years

## 6.5 Outcome measures

The **primary** outcome measure was the incidence of cardiovascular events per over-50 year population (overall number of events/patient years) during the two years of the study. Cardiovascular events are defined in the Box. The **secondary** outcomes were the difference in proportion of the over-50 year population in each of the Groups between the two arms at the end of the study. This would be measured as the mean of the last three eight-weekly data captures. I also measured the change in proportion from baseline.

**Box: Definition of a cardiovascular event**

A new diagnosis of ischaemic heart disease  
A new diagnosis of cerebrovascular disease  
A myocardial infarction (patient may already be known to have ischaemic heart disease)  
A transient ischaemic attack (TIA) (patient may already have cerebrovascular disease)  
A stroke (patient may already have cerebrovascular disease e.g. past stroke or TIA)  
Sudden death from cardiovascular disease

An entry of 'Angina' in someone who is already known to have IHD was not a new event unless it were associated with acute admission for a coronary artery procedure e.g. angioplasty. However it *was* a new event in someone who did *not* already have diagnosed IHD. An elective coronary artery procedure was not counted as a cardiovascular event.

## 6.6 Sample size calculation

### 6.6.1 Outline estimate of sample required

The incidence of cardiovascular events was the primary outcome used for the power calculation. Assuming a cardiovascular event rate of 1260 events per 100,000 person-

years (all ages) in the control arm (9, 10) and 10% lower event rate in the intervention arm (rate ratio of intervention to control of 0.9) I estimated that a total sample of about 70,000 patients followed up for 2 years would give 80% power at 5% significance (two-tailed), allowing for 15% withdrawal (11). This calculation was based on all age event rate as I was unable to find an event rate specifically for the over 50s. The intervention was applied to the over 50 year population and I measured the outcome in this age group only. I assumed that the cardiovascular event rate followed a Poisson distribution, in keeping with other studies of vascular outcomes such as OXVASC (10).

### **6.6.2 Individual or cluster randomisation?**

I considered the option of cluster randomisation, which had been raised by two local reviewers of the e-Nudge protocol and also during the seminar that I gave at ScHARR, discussed in Chapter 5. This approach removes any risk of contamination of the intervention into the control arm and is generally preferable for trials of complex interventions, but usually requires a significantly (and often prohibitively) larger sample size. I estimated the necessary inflation of the sample (the ‘design effect’) due to clustering (12).

The design effect is related to the cluster size and the intra-class correlation coefficient (ICC). The ICC can be estimated using the formula:

$$\text{ICC} = \text{variance between clusters} / (\text{variance between} + \text{variance within clusters})$$

If clustering effects are marked (giving a high ICC) then observations within the cluster have a tendency to be similar, and a higher proportion of the variability is between clusters. More clusters are then required to provide the same power. If the ICC is low then the design effect is reduced. In the extreme case the ICC would be zero, indicating that observations of the intervention effect on all individuals in the study are

independent measures of the effect and unrelated to the cluster to which the individual belongs.

The formula for the inflation in sample size to account for clustering is:

$$N^+ = N(1+(m-1)ICC)$$

Where:

N+	=	sample size following inflation
N	=	initial sample size
m	=	cluster size
ICC	=	Intra-class correlation coefficient

When designing the trial I did not have a reliable estimate of the ICC related specifically to this area of care. However it was clear that m would inevitably be large. The mean number of patient records to be randomised per practice was estimated using Primary Care Trust data to be 2355 based on the mean over 50 year population in all practices in South Warwickshire during 2005. Even if I interpreted ‘m’ to be the number of patients identified in the groups by the e-Nudge rather than the whole over-50 year population, and if by excluding the large Group 2 whose size was defined arbitrarily, I was still left with m=111 as a minimum. In fact these assumptions were not strictly valid (as the primary outcome denominator was the over-50 year population, not the population identified in the e-Nudge groups), but in an early discussion document I derived the necessary sample sizes based on this value for m and a range of ICC values taken from the published literature. I also sought informal advice on this from Sandra Eldridge of Queen Mary’s University of London, who has special expertise on cluster-randomisation. She suggested that a value of around 0.03 might be appropriate for a trial of this type. Table 6.1 gives the values obtained.

ICC	Source	Design effect	Necessary sample size
Zero (disregards clustering)		1	70,000
0.0036	Kerry and Bland (12, 13)	1.4	98,000
0.03	Advice from Sandra Eldridge	4.3	301,000
0.045	Kinmonth et al (14)	5.95	416,500
0.0644	Fahey and Peters (for UK) 15)	8.1	567,000
0.199	Cosby et al (for mean systolic blood pressure) (16)	21.9	1,533,000

*Table 6.1: A range of possible values for the intra-class correlation co-efficient and their implications for the e-Nudge sample required based on  $m=111$ .*

This very conservative approach (i.e. using the above assumption for the value of  $m$ ) demonstrated that only if the ICC were extremely small would cluster-randomisation be an option given the practice capacity available. I considered whether there might be some way of estimating the ICC using locally available data. I approached Greg Wells, Consultant in Public Health at South Warwickshire Primary Care Trust for data on the recording of vascular diagnoses across practices in the region. He provided prevalence estimates of coronary heart disease and stroke/TIA at the practice level as well as the indirectly standardised prevalence ratios (Figure 6.4). Whilst these data were different from the outcomes of a trial, they were a potentially useful indicator of the extent to which practice specific processes might influence the recording of cardiovascular events, my primary outcome measure.

The indirectly standardised prevalence ratio (ISPR) is the ratio of observed/expected prevalence of the condition. Expected prevalence is based on PRIMIS data (17) and is adjusted for practice demographics. If all practices were recording the expected number of cases electronically then the crude prevalence would vary by practice but the ISPRs would all be about 100 if variation in practice

demography had been sufficiently accounted for in determining expected prevalence. Whilst this is an imprecise process, practices varied in their ISPRs from 60.5 to 124 for CHD (a 2.1 fold difference) and from 17 to 179 for Stroke/TIA (a 10.5 fold difference, although one of these practices was quite an extreme outlier).

I concluded from this that despite recent improvements in the recording of these conditions described in Chapter 2, the observed variation was likely to be at least partly a reflection of practice-level processes, and not just the risk of the condition itself, particularly for stroke/TIA. Important factors might include the tendency of the practice team to investigate possible vascular symptoms, the handling of hospital discharge reports, the process through which neurovascular or chest pain clinic referral outcomes were recorded, and the threshold for attributing symptoms to vascular events within the practice team. Whilst there is variation in the practices of all clinicians across UK primary care, these tendencies might be influenced by team communication and shared learning at the practice level.

An individual patient's risk of being on a vascular disease register was probably determined therefore not only by the actual presence of the condition but also by the practice that he or she happened to be registered with. This provided indirect evidence that clustering of recorded vascular data would be significant. It was probably unrealistic to assume a low ICC for e-Nudge study outcomes, and the option of individual randomisation was taken.

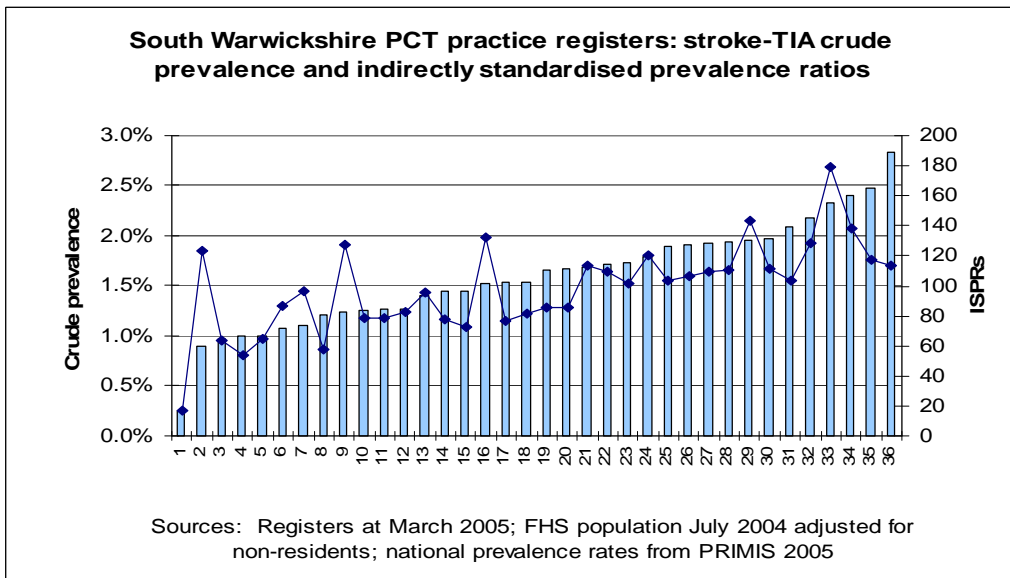
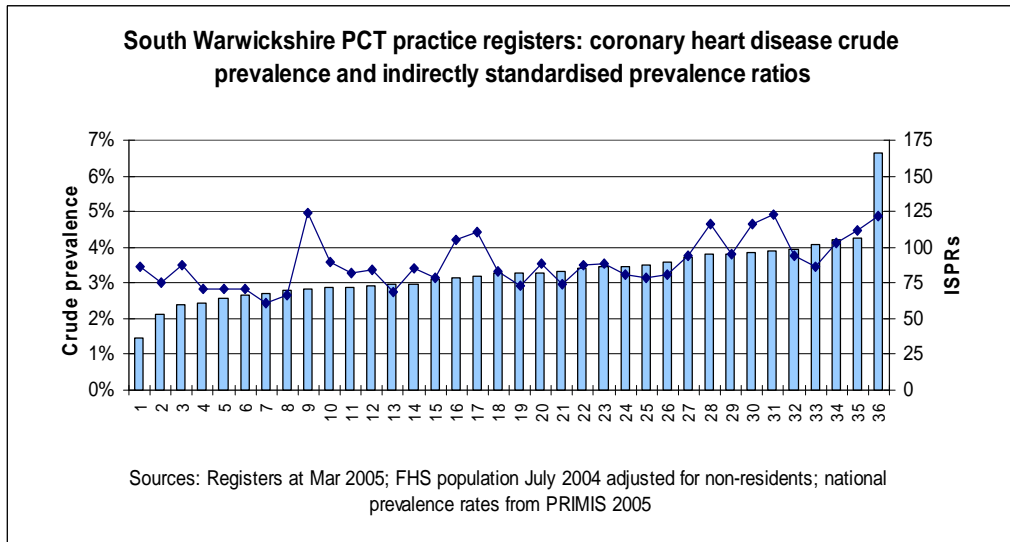


Figure 6.4: Crude prevalence (columns) and indirectly standardised prevalence ratios (joined points) for Coronary Heart Disease and Stroke/TIA among the 36 practices of South Warwickshire in March 2005. The practice numbers are unrelated to those used for e-Nudge trial practices elsewhere in this thesis.

## 6.7 Recruitment

Practices using the EMIS LV clinical system were identified from Primary Care Trust sources of South Warwickshire, Coventry, Rugby and North Warwickshire. This was required to install the e-Nudge software, but no other eligibility criteria were applied. EMIS supply clinical and administrative software to nearly 60% of UK practices, and 80% of their systems use the LV version. The majority of EMIS LV practices in



Coventry and Warwickshire (41 out of 71 available practices) were invited to take part and all that were willing were accepted into the trial. An invitation letter was sent to the senior partner (unless another GP was more clearly the lead on cardiovascular disease, or research). I telephoned practice managers initially to prime them that an invitation was about to be sent, and to confirm that the practice was still running EMIS LV. Positive responses were followed up through meetings with practice managers and in most cases presentations to general practitioners.

## **6.8 Randomisation and allocation concealment**

As discussed above, randomisation was at the level of the individual patient record. The e-Nudge software automatically randomised registered patients within each practice to intervention and control arms depending on whether the last digit of the ten digit National Health Service (NHS) number was odd or even. This number is a unique identifier allocated to all individuals registered with the NHS and is generated using an algorithm which takes no account of age, socioeconomic group, or any other factor relevant to cardiovascular risk. The 10<sup>th</sup> digit is calculated according to the Modulus 11 algorithm (18) and serves as a 'check digit' to confirm the number's validity.

New patients registering with a practice during the study were randomised as soon as the NHS number was available in the record. Throughout the trial users of the e-Nudge were kept unaware of the odd/even rule, but if an alert appeared on opening a record it would be evident that the patient was in the intervention arm. It was made clear to users at the outset that patients who did not trigger alerts were not necessarily at low cardiovascular risk, as they might simply be in the control arm.

## **6.9 Extracting and cleansing of outcome data**

### **6.9.1 Primary outcome**

Data on the primary outcome (CVD event rates) were collected after the first year of the trial (for the purposes of data monitoring) and at the end of the trial. This involved searches carried out on each practice database either by the Research Nurse Rachel Potter (for the first year) or by myself (for the second year). The standard operating procedure used for this collection process is given in the Appendix. It was designed to be as straightforward as possible so that the process used for each year was the same. For each identified patient experiencing a CVD event during the year, the entire 12 month period was examined to count exactly how many events had occurred. In the trial protocol, we had specified that this process would only be necessary for those who had apparently experienced more than one event during the study. But in practice this task was greater than expected. First of all, it proved impossible to build searches using EMIS LV that would identify only those with more than one event. Secondly, the problem of duplicate entries for the same event was clearly commonplace. Thirdly, the recording of an event that had in fact occurred outside the trial period was sufficiently common that a check on all recorded events was necessary.

### **6.9.2 Secondary outcomes**

Data on the secondary outcomes (Group proportions) were generated automatically by the e-Nudge software. Every eight weeks the e-Nudge recorded the numbers of patients in each group (for both trial arms) and stored these data away as Text files in the 'shared' folder of the practice main server. It also recorded the number registered in the over 50 year practice population as the denominator at that particular time point. As specified in the protocol, the average of the final three 8-weekly data collections at the end of the 24 month trial period was used as the outcome group proportion.

### **6.9.3 Quality assurance**

Recording of cardiovascular outcomes is prone to several sources of error recognised in the trial protocol (1). Not all cardiovascular events result in a new coded entry into a primary care record, and sometimes a single event is recorded more than once using different codes or entry dates. When a patient dies the need to record the final event electronically is no longer a priority for clinical care, although it is usual practice to do so. For these reasons every electronic record identified in the primary outcome searches was examined. I also carried out a small sub-study in four practices to check whether any sudden cardiovascular deaths had been missed. For this sub-study, extra code groups were included in the searches to increase the retrieval of cases: 'Death administration,' 'On examination – Dead,' and all of their lower level codes. The results are given in the next chapter.

### **6.9.4 Changes to the trial protocol**

In the original protocol, patients with existing CVD or diabetes whose blood pressure or serum cholesterol were out of the QOF target were to be identified as Group 1. However, screen alert messages were introduced to all EMIS systems to support the QOF just before the start of the trial. This group was therefore withdrawn from the trial.

The e-Nudge was initially designed also to identify individuals with possible undiagnosed diabetes based on previous raised blood glucose measurements. A number of such individuals were identified at baseline following installation of the e-Nudge software and during the preparatory work. This led to a nationwide QRESEARCH survey to demonstrate that such patients are identifiable across the UK (19), and the result was the introduction of a new software module to all EMIS systems nationally to support early diabetes detection, including of course both control and intervention patients in the e-Nudge practices (20). This group was therefore withdrawn from the e-

Nudge within the first six months of the trial. The QRESEARCH survey is described in more detail in Chapter 8.

During practice visits I discussed practical issues surrounding the usability of the software which were noted and acted on. After approximately nine months the wording of the screen messages was shortened in response to practice feedback as discussed above.

### **6.9.5 Statistical analysis and intention to treat**

Analysis was carried out using STATA 10 and SAS software. For the cardiovascular event rates the rate ratio (intervention/control) was derived with a two-tailed 95% confidence interval. We used standard likelihood inference techniques for Poisson counts (21). The group proportions were compared using Chi<sup>2</sup> tests to derive two-tailed P-values. We analysed data from all patients whether or not their computer record had been accessed by primary care staff during the trial (i.e. whether or not they had actually been exposed to the intervention).

One practice withdrew from the study after less than six months, but consented to its data being included in the analysis. However the automatically captured group data were no longer available from this practice after the software was switched off, so only the cardiovascular event rate data were used as part of the final analysis. In another practice, a failure of data capture occurred at baseline and the earliest data available at this site were extracted after the intervention had been in place for 25 days.

## **6.10 Summary**

The design of the e-Nudge trial was tailored to the pragmatics of routine primary care. In particular, the screen reminders took the same format as the QOF alerts, but perhaps most significantly, they drew on the *most recent risk factor data available* in the record to identify potentially at risk individuals. This approach supported contemporary (and

more recent) guidelines towards case finding for CVD risk in a situation where pre-treatment values (of serum cholesterol and blood pressure) are often unavailable, whether or not they are considered preferable to current values as a means of defining this risk.

Two of the original six e-Nudge groups were withdrawn from the intervention for practical reasons. The first of these withdrawals resulted from the arrival of identical alerts into routine care as part of the QOF during 2005/06. The second involved the identification of patients with possible undiagnosed diabetes, and led on to a separate project resulting in new reminders established nationally as part of routine care for all EMIS users.

The next chapter will detail the results of the trial recruitment, the baseline data extraction, the quality assurance sub-study, and the effect of the intervention on primary and secondary outcomes.

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## Chapter 7: Results of the e-Nudge trial

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### 7.1 Introduction

The general hypothesis tested through the e-Nudge trial was that an automated system of electronic reminders operating in the environment of routine primary care could usefully support CVD prevention in UK general practice. A number of more specific hypotheses defined the trial outcomes. These included not only clinical events but also process measures relevant to the estimation and control of cardiovascular risk. Some of the following text is adapted from the e-Nudge trial final report accepted by the *British Journal of General Practice*.

### 7.2 Practice recruitment and study population

#### 7.2.1 Approaching practices

Each practice was offered a visit and presentation to the general practitioners to explain the trial and gain their written consent. Fourteen practices accepted this invitation, four were recruited through a less formal meeting with the key GP partner, and one accepted without the need for a visit (other than to meet the practice manager, which happened in all cases). The 19 practices had a combined list size (all ages) of approximately 121 000, of which 38 147 were in the over 50 year age group at baseline. The practices were based in diverse settings including rural, suburban and inner city environments. The practice list sizes varied from fewer than 2000 to greater than 14,000 patients, and from single handed practitioners to large group practices with more than six partners. I estimated 77 208 person years of follow up over two years (38 382 for intervention participants and 38 826 for control participants). Recruitment began in May 2006 and was completed in September 2006. The first practices started using the e-Nudge on 6<sup>th</sup>



June. A total of four waves of installation occurred during the summer of 2006 each involving four or five practices.

### **7.2.2 Revision of the sample size calculation**

The original sample size calculation used an expected CVD event rate based on ‘whole population’ level incidence data (from the British Heart Foundation (1) and the OXVASC study (2)). With statistical advice, I initially estimated that 70,000 *of all ages* were required, and this is the figure published in the trial protocol (3). This figure appeared to be comfortably reached by the 121,000 patients registered with the 19 practices. After the trial began however, new statistical advice suggested that the 70,000 figure was in fact that required for the over-50 year population alone. This left me in a dilemma as the study appeared to be under-powered for the primary outcome. However, I assumed that a significantly higher event rate in this older age group might well offset this reduction in power, and I decided to continue. It would have been very difficult to have recruited sufficient numbers for this re-estimated sample with existing resources, and the (perhaps equally important) secondary outcomes were likely to be very adequately powered.

### **7.2.3 Age distribution**

The age structure of the over 50 year population in each practice is given in Table 7.1 and Figure 7.1. This demonstrates the range of practice list sizes, but practices also varied considerably in the proportion of the over 50 year population that were over 75 years with range 0.09 to 0.51.

Practice No	Number of patients 50-74 years	Number of patients over 75 years	Proportion over 50 years also over 75 years
1	958	231	0.19
2	247	137	0.36
3	1902	837	0.31
4	837	195	0.19
5	1629	596	0.27
6	629	144	0.19
7	2807	900	0.24
8	2454	941	0.28
9	2146	785	0.27
10	2614	796	0.23
11	1586	428	0.21
12	2161	789	0.27
13	2128	636	0.23
14	846	321	0.28
15	1301	330	0.20
16	826	266	0.24
17	673	700	0.51
18	1257	125	0.09
19	471	123	0.21

Table 7.1: Numbers of patients in age groups 50-75 years and over 75 in each practice

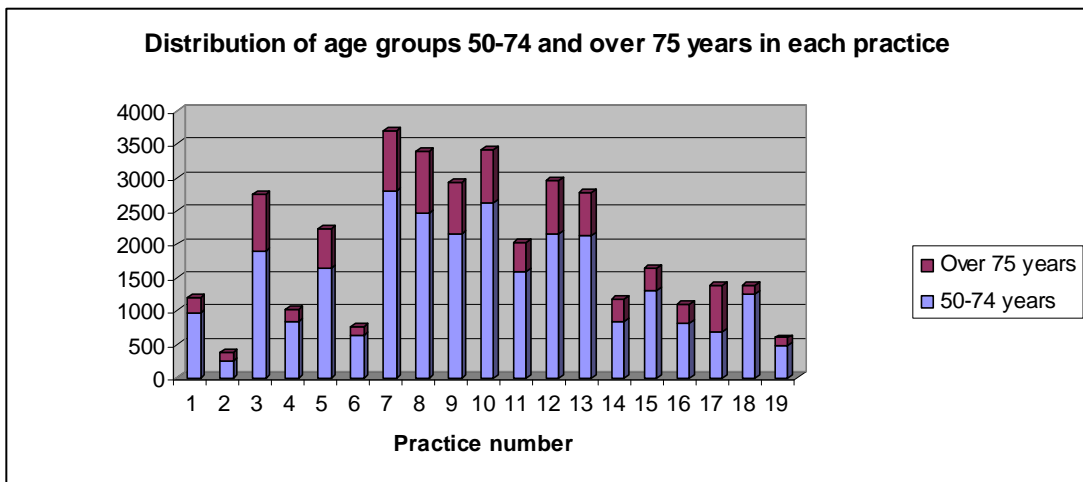


Figure 7.1: Numbers of registered patients identified 50-74 years and over 75 years in each practice.

The e-Nudge population was very similar to the overall UK population taken from the Office of National Statistics (Figure 7.2), but with a slightly smaller 50-74 year population. The estimates for the e-Nudge 0-49 year age groups were not known quite

as accurately as those of the over 50 years group, whose value at baseline was known exactly through automated data capture.

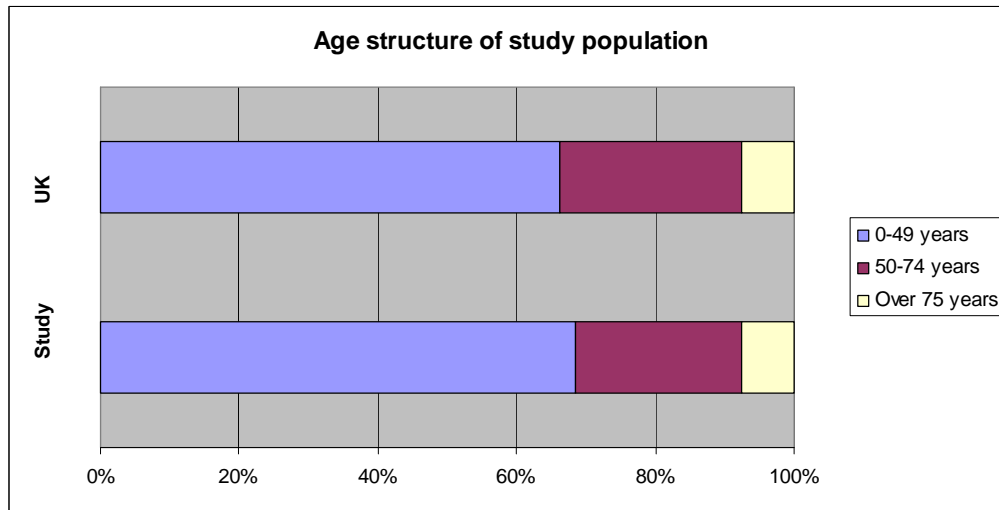


Figure 7.2: Age structure of the study population and background UK population.

#### 7.2.4 Deprivation and coronary heart disease standardised mortality ratios

Demographic variables were obtained from Primary Care Trust sources for the study population. These demonstrated a range of coronary heart disease indirectly standardised mortality ratios (SMR) ranging from 74 in Stratford to 110 in North Warwickshire. The Index of Multiple Deprivation scores for the Super Output Areas of the practices ranged from 8.35 in Stratford to 67.03 in Coventry, whilst the Health Deprivation and Disability Score ranged from -0.79 to 1.86. All four quartiles of the deprivation scores for England were sampled during the recruitment of practices (Table 7.2).

<b>Practice Number</b>	<b>Index of Multiple Deprivation</b>		<b>Health related Deprivation</b>		<b>CHD SMR</b>
<b>Stratford area</b>	<b>Practice score</b>	<b>Quartile</b>	<b>Practice score</b>	<b>Quartile</b>	<b>74</b>
1	8.35	4	-0.68	4	
6	10.27	3	-0.78	4	
15	9.83	3	-0.61	3	
19	8.95	4	-0.92	4	
2	9.95	3	-0.79	4	
<b>Warwick area</b>					<b>75</b>
8	21.14	2	0.12	2	
7	14.65	3	-0.26	4	
<b>Coventry</b>					<b>89</b>
10	11.63	3	-2.8	4	
18	51.26	1	1.29	1	
3	23	2	0.46	2	
11	43.69	1	0.92	1	
16	67.03	1	1.86	1	
9	23.94	2	0.28	2	
17	55.52	1	1.75	1	
<b>Rugby</b>					<b>94</b>
4	13.64	3	-0.44	3	
12	18.69	2	-0.1	3	
<b>North Warwickshire</b>					<b>110</b>
14	27.32	2	0.57	2	
5	31.44	1	0.8	1	
13	28.99	2	0.66	2	

*Table 7.2: Deprivation indices for the super output areas of the trial practices and Coronary Heart Disease indirectly standardised mortality ratios (based on ICD-10 I20-I25). The deprivation quartile 1 is the most deprived, and 4 is the least deprived.*

### **7.3 Baseline characteristics of control and intervention arms**

The numbers identified at baseline in e-Nudge Groups A-D are given in Table 7.3.

There were no significant differences between the trial arms, except for Group B (originally Group 2), where more were identified in the intervention arm, although this was of borderline significance. This was the group that identified individuals with

missing data but potentially at risk of CVD. I discussed this with our statistician Dr Tim Friede. He advised that as the group was only one of numerous groups, this finding did not necessarily question the validity of a randomisation technique that was very unlikely *a priori* to be biased. Group 2/B was defined in terms that were essentially arbitrary (e.g. the cut off values for risk factor thresholds). Alternative choices for these parameters would have identified overlapping but non-identical groups, and each would have a slightly different control/intervention ratio. It happened that the group definition that I chose displayed a small but significant (at the 5% level) excess of intervention patients. All the other groups, as well as the original Groups 1 and 5 that were later excluded from the trial (see Chapter 8) had baseline ratios that were not significantly different from unity.

I was unable to measure any other characteristics of the groups identified (such as age, sex, or other risk factor distributions), as the e-Nudge was designed only to record the actual numbers. Nevertheless these figures provided an estimate of the relative proportions with adequate data for a risk estimate (5.93%) compared with those who would require further data collection to support an estimate but might be at high risk (26.40%). In a brief report to the *British Journal of General Practice* (4) we presented these data as a cross-sectional survey and discussed the possible implications for NHS priorities and resources. I was also able to measure the proportion of the over 50 year population in the original Group 1, those with existing cardiovascular disease or diabetes whose blood pressure or cholesterol levels were out of target for the QOF (9.10%). This demonstrated that the population at immediately identifiable risk (based on CVD risk factors that are only partially modifiable) is significantly smaller than the population with clearly modifiable risk factors. This might be relevant to the issue discussed in Chapter 3 over the appropriate allocation of resources. The data presented in Table 7.3 followed a minor correction to those published in *BJGP* (required due to a data capture problem at baseline in one practice) but this did not significantly affect the proportions identified.

The finding that most patients in the study population require further data collection is unsurprising and concurs with the findings of Marshall et al in the Sandwell project (5, 6). The proportion identified in Group A (those with identifiably high risk) might be compared with the number *expected to be at high risk in the population* (if all patients were invited for completion of data and then risk assessed). This figure is given as 22.8% for men and 7.9% for women in the JBS2 for the 40-75 year age group at the >20% over 10 year level. Increasing the visibility of this group to practice teams was the function of the e-Nudge intervention, by targeting those most likely to produce a raised risk level if their risk profiles were completed (Group B) to raise the prevalence of identifiably raised risk (Group A).

	<b>Numbers identified at baseline</b>	<b>Proportion of over-50 year population (%)</b>	<b>Intervention</b>	<b>Control</b>	<b>P value (H<sub>0</sub> = no difference between arms)</b>
<b>Total Pop<sup>n</sup></b>	38147	100	18 912	19 235	0.099
<b>Group A</b>	2 261	5.93	1 124	1 137	0.894
<b>Group B</b>	10 069	26.40	5 079	4 990	0.043
<b>Group C</b>	1044	2.74	525	519	0.641
<b>Group D</b>	170	0.45	81	89	0.614

*Table 7.3: Numbers identified and proportions of the over-50 year population in each Group at baseline.*

#### **7.4 Trial denominator populations**

Following installation of the e-Nudge software, the over 50 year denominator population was measured as discussed above. This denominator changed during the trial due to natural migration effects (new people registering with practices and those

moving away from the area). In addition, one practice withdrew from the trial after less than 6 months. For the purposes of measuring the primary outcome (CVD event rates), for which I was able to include this practice (for the purpose of intention to treat), I calculated the mid-trial denominator population on the basis of all 19 practices. For the secondary outcomes (Group proportions) I was unable to include the practice that withdrew as the e-Nudge was switched off and therefore no longer able to generate the eight weekly reports. The result was that three denominator populations were used: the baseline denominator, the mid-trial denominator, and the final denominator at the end of the trial. Table 7.4 provides these denominator data.

Baseline population (19 practices)			Estimated mid-trial population for primary outcome (19 practices)			Outcome population for secondary outcomes (18 practices)		
Int	Contol	Overall	Int	Contol	Overall	Int	Contol	Overall
18912	19235	38147	19191	19413	38604	18021	18071	36092

*Table 7.4: Denominator population values during the e-Nudge trial. For the purposes of Intention to Treat the data from all 19 practices were used for the primary outcome measure (cardiovascular event rates), and to estimate the mid-trial population even though by this time one practice had withdrawn.*

## 7.5 Primary outcome: cardiovascular event rates

A total of 2121 individual records were examined in the search for new events during the two years of the trial. This process detected 930 events occurring in the trial population. In year one 492 events occurred in 454 individuals (21 experienced two events, 7 experienced three, one experienced four). In year two 438 events occurred in 412 individuals (19 experienced two, 2 experienced three, and one experienced four). Because the annual searches were run separately it is not known how many individuals affected in year 1 were also affected in year 2.

The cardiovascular event rates in the intervention and control arms are given in Table 7.5. The rate ratio was 0.96 [95% confidence interval 0.85 - 1.10], two tailed

P=0.59 indicating a non-significant difference. These confidence intervals were estimated using an inference technique for Poisson counts described by Ng and Tang (7).

Arm	Cardiovascular Events			Patient years of follow up	Rate/100,000 population/year
	Year 1	Year 2	Total		
<b>Intervention</b>	235	219	454	38 382	1183
<b>Control</b>	257	219	476	38 826	1226
<b>Overall</b>	492	438	930	77 208	1205

*Table 7.5: Cardiovascular event rates in the two arms of the trial*

## **7.6 Secondary outcome measures: proportions in Groups A, B, C and D**

The overall proportion of the over 50 year trial population identified in each arm at the end of the trial is given for the four e-Nudge groups (A-D) in Table 7.6. The differences (intervention-control) in this outcome for each group at the end of the trial are given in the final row. These were the secondary outcome measures for the trial. I also measured change from baseline for each group.



	<b>Percentages in groups (number in parentheses)</b>			
	<b>Group A</b>	<b>Group B</b>	<b>Group C</b>	<b>Group D</b>
<b>Intervention</b>				
Baseline (N=18912)	<b>5.94</b> (1124)	<b>26.9</b> (5079)	<b>2.78</b> (525)	<b>0.43</b> (81)
Outcome (N=18021)	<b>8.91</b> (1606)	<b>19.4</b> (3502)	<b>0.55</b> (99)	<b>0.33</b> (59)
Absolute change (%)	<b>2.97</b>	<b>-7.48</b>	<b>-2.23</b>	<b>-0.10</b>
<b>Control</b>				
Baseline (N=19235)	<b>5.91</b> (1137)	<b>25.9</b> (4990)	<b>2.70</b> (519)	<b>0.46</b> (89)
Outcome (N=18071)	<b>6.97</b> (1260)	<b>23.1</b> (4177)	<b>1.01</b> (183)	<b>0.31</b> (56)
Absolute change (%)	<b>1.06</b>	<b>-2.83</b>	<b>-1.69</b>	<b>-0.15</b>
<b>Intervention-Control difference at outcome [95% confidence interval]</b>	<b>1.94</b> [1.38; 2.50] P<0.0001	<b>-3.68</b> [-4.53; -2.84] P<0.0001	<b>-0.46</b> [-0.64; -0.28] P<0.0001	<b>0.02</b> [-0.10; 0.13] P=0.7679

*Table 7.6: Group proportions in the baseline and outcome populations by trial arm. (Group A: Patients who are not known to have cardiovascular disease or diabetes, are under 75 years old, and whose most recent Framingham variable values indicate that their CVD risk level is raised. Group B: Patients who are not known to have cardiovascular disease or diabetes, are under 75yrs old, and whose risk profile is incomplete – more information is required to perform a risk estimate - but whose CVD risk would be greater than 20% if the “assumed” values of the missing factors were used. Group C: Patients with CVD but not diabetes, who have not had a blood glucose measurement in the past three years. Group D: Patients who are not known to have cardiovascular disease or diabetes, are greater than 75yrs old and who have persistently elevated blood pressure based on the three most recent consecutive readings.)*

The percentage increases and reductions in this table are absolute rather than relative changes. A significant increase in the number identified in Group A (those whose raised risk was identifiable due to adequate risk factor data) occurred with a corresponding reduction in Group B (those with incomplete profiles but potentially at risk). A reduction was also seen in Group C (those with CVD but no recent blood glucose measurement). Whilst there were background improvements in the control population during the study, the improvements in the intervention arm were

significantly greater for these three groups. However no significant change was seen in intervention patients over 75 years with persistently raised blood pressure (Group D).

## **7.7 Practice level changes in group proportions**

Considerable variation was seen between practices in the impact of the e-Nudge on group proportions. The change in proportion of intervention patients identified in the four groups in each practice during the trial is an indicator of the degree to which different practice teams responded to the reminders. For example, the median absolute increase in the Group A proportion was 3.45% with range -1.3% to 8.2%. The median absolute reduction in the Group B intervention population was 5.1% with a range 2.5% to 20.3%. These values are given in Table 7.7 for all the practices. For Group A, 8 out of 18 practices demonstrated change that was not significant at the practice level. Changes in Group B proportions were significant in all but three practices. Groups 4/D and 6/C are not tabulated as the numbers are small and generally non-significant at the practice level.

Practice	Group A				Group B			
	Baseline (%)	Outcome (%)	Change (%)	P value	Baseline (%)	Outcome (%)	Change (%)	P value
1	4.2	11.5	7.3	<0.001	42.7	27.3	-15.4	<0.001
2	5.3	6.3	1	0.207*	30.2	27.7	-2.5	0.098*
3	6.8	10.5	3.7	<0.001	24.4	13.3	-11.1	<0.001
4	4	12.2	8.2	<0.001	38.5	18.2	-20.3	<0.001
5	5.8	9.9	4.1	0.072*	21.5	12.2	-9.3	0.004
6	10.9	9.7	-1.2	0.519*	22.4	19.1	-3.3	0.163*
7	8.7	7.4	-1.3	0.194*	26.1	23.4	-2.7	0.094*
8	4.8	7.5	2.7	0.059*	18.3	13.5	-4.8	0.025
9	6.3	12	5.7	<0.001	21.9	16.8	-5.1	0.002
10	7.2	8.8	1.6	0.066*	16.5	13	-3.5	0.009
11	5.6	7.6	2	0.024	21.7	18.3	-3.4	0.023
12	5.3	9.1	3.8	0.001	33.4	20.4	-13	<0.001
13	5.1	8.3	3.2	0.001	27.6	23.8	-3.8	0.017
14	5.1	10	4.9	0.001	28.2	17.6	-10.6	<0.001
15	2.9	7.3	4.4	<0.001	42.1	29.6	-12.5	<0.001
16	8	9.8	1.8	0.511*	18.3	10.4	-7.9	0.038
17	7.3	12	4.7	0.007	24.4	16.4	-8	0.001
18	4.5	5.4	0.9	0.582*	9.8	5.5	-4.3	0.020

Table 7.7: Intervention patients identified as proportion of the over 50 year population at baseline and after two years in the eighteen practices that completed the trial for groups A and B. Those marked \* are not significant at the 5% level.

However, some of this change was due to secular (non-study related) effects also influencing the control population, improving adequacy of CVD risk factor data during the trial. The Box gives a vignette of how the e-Nudge influenced care in the practice with the median list size.

**Box: Example of how the e-Nudge helped a practice identify patients for CVD risk reduction**

The median list size practice in this study had 1381 registered patients over 50 years at baseline, of which 681 were in the intervention arm.

After installing the e-Nudge, 35 patients were identifiable at raised cardiovascular risk based on existing data (Group A) whilst 192 patients were possibly at risk but required further data for a risk estimation (Group B).

After two years of using the e-Nudge during routine care there were 65 patients identifiable at risk, whilst the number requiring further data had fallen to 114 patients. Lists were available of these groups making them easy to target for risk reduction interventions including lipid lowering therapy, or completion of risk profile data.

Some of these changes would have happened anyway due to background improvements in data quality. However, the 700 control patients in this practice showed a lower rise in Group A (from 38 to 50 patients) and a fall in Group B of only 38 (from 211 to 173).

## 7.8 Quality assurance sub-study

As described in Chapter 6, a small sub-study was undertaken in four practices to assess the rate of fatal unrecorded events. In addition to the 73 events already confirmed in these four practices through the standard searches, a further 34 records were then identified (that included deaths from all causes). When these extra notes were examined, two definite ‘missed’ cardiovascular deaths were identified. A further two possible missed events were found, but it was not clear from the information available whether these satisfied the definition of a cardiovascular event used in this study. Depending on whether we assume two or four missed events, this suggests that either 2.6% or 5.2% of events are missed by the standard searches. This error should apply equally to both arms of the trial. This proportion is similar to the rate of ‘unclassifiable deaths’

measured at 3% in the OXVASC study (2), which estimated CVD events using a combination of 'hot' and 'cold' pursuit methods. The OXVASC investigators used the term 'unclassified' to mean that the CVD event could not easily be attributed to a particular cardiovascular territory (coronary, cerebral, or peripheral), rather than questioning whether or not it was vascular in nature. In our study, the undetermined events were not necessarily vascular, but no other cause was evident on thorough perusal of the medical records (including hospital letters in the primary care notes), and no evidence for a final illness was found, so that the event was certainly acute, if not definitely vascular.

## **7.9 Intention to treat**

I applied the intention to treat principle (ITT) in two ways through this study. First of all, the e-Nudge was in principle applied to the whole over 50 year population, but only those presenting to the practices were likely to be exposed to the intervention, as the screen reminder messages required that notes were accessed by practice staff. This was likely to happen only if the patient interacted with the practice in some way. There was little evidence through my field notes and discussions with practices that the lists of intervention patients had actually been used systematically. However, the denominator for the primary and secondary outcomes was the entire over-50 year population, not simply the subgroup that had been exposed.

Secondly, I applied ITT in measuring the primary outcome, by including the cardiovascular event rate data from the practice that had withdrawn after less than 6 months. This practice population had spent most of the two year study period with the e-Nudge switched off, but its data were included in the primary outcome analysis. It was impossible for technical reasons to include them in the secondary outcomes, as the group proportion data required the e-Nudge to store the information automatically in the practice's main server.

## 7.10 Conclusions of the e-Nudge trial

The e-Nudge trial demonstrated a significant effect of automated electronic reminders on processes of care related to CVD risk reduction. These processes involved specifically the adequacy of data relevant to cardiovascular risk in general practice. Interpretation of electronic data is only one element of the clinical assessment of CVD risk, but it is an important one in current practice. Assessing risk of CVD is only possible through the algorithmic processing of information, which is very amenable to software support for the clinician. Processing of routinely collected data not only facilitates targeted CVD risk reduction interventions, but also the completion of risk factor profiles in those most likely to benefit from this exercise. It might be hoped that given a longer timescale the benefits on processes of care would result in improvements in hard clinical outcomes, but it was not possible to demonstrate such an effect within the two year duration of the trial. Variation in response to the reminders between practices was quite noticeable. This finding is in keeping with the results of the systematic review described in Chapter 4. Further work is required to clarify the organisational and contextual factors that determine responsiveness in this particular clinical area.

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## Chapter 8: The research process

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### 8.1 Introduction

The e-Nudge trial tested the effects of applying a cardiovascular risk algorithm to a practice population and flagging up identified individuals during routine care. In designing and implementing the trial I was aware that cardiovascular prevention is delivered at a personal as well as at a practice based level. Individual needs and priorities are bound to influence this activity. The sociological aspects of CVD risk reduction became important to the research process and are probably important also for addressing the CVD prevention problem in general practice, although this topic is too broad to investigate within this thesis. This chapter discusses insights gained through the practicalities of conducting the e-Nudge research.

It might be assumed that the identification of raised cardiovascular risk in an environment where a clinician is immediately available to prescribe treatments known to reduce this risk would reliably influence professional behaviour, patient choices, and perhaps ultimately clinical outcomes. The e-Nudge intervention, as discussed in Chapter 7, had a significant impact on process outcomes but the variation in this effect between practices was wide. At the outset I postulated that a number of factors might influence receptiveness to its flagging mechanisms. These included both clinician and patient factors, as well as factors related to the practice environment and the prevailing organisational context of primary care under the newly established QOF. I took detailed field notes throughout the PhD project together with a number of informal surveys in a test practice. I also carried out a series of in-depth interviews with members of the public registered with one of the e-Nudge practices. The field notes are the basis for much of the detail described in this chapter. The interview transcripts were subjected to a thematic analysis, and these are given in the Appendix.



## **8.2 Designing the e-Nudge software**

### **8.2.1 The software platform**

EMIS's Medical Director David Stables chose to programme the e-Nudge using their LV software platform, a version of the EMIS clinical system that is older than their GV, PCS, and (most recent) EMIS-Web systems. EMIS-Web is a web-based platform that can support either LV or PCS, but was not sufficiently developed to be available to us when the e-Nudge was originally conceived. Few EMIS practices use GV as this was superseded by PCS but the majority (80%) were still using LV at the time of the trial. I was familiar with the LV system in my previous North Yorkshire practice. The LV version of EMIS is supported by an older operating system but retains certain features (including search functions) that are considered superior to the newer PCS. A Primary Care Trust source told me that many of the practices in the city of Coventry began using EMIS LV following a wave of computerisation during the early 1990s, in which this version was encouraged in that area. Of the options available LV was certainly the commonest and therefore offered the best recruitment potential.

### **8.2.2 Choice of CVD risk algorithm**

During the e-Nudge trial the QRISK algorithms were published, and an ongoing debate began over the relative merits of these new, UK population based algorithms compared with the long established Framingham equation. However the design phase of e-Nudge preceded these developments and the question at this stage was simply over which 'version' of Framingham to use. I was aware that the approach recommended in the back sheets of the British National Formulary (a widely circulated publication updated every six months) utilised risk charts that were essentially based on Framingham but simplified to include age bands rather than individual ages. I found it difficult to find a

published source for the programming behind these charts, or for other electronic risk calculators that were available. One of these, designed by Hingorani and Vallance was published in the British Medical Journal (1) and had been recommended in the NSF for CHD 2000 (2). I had originally contacted Aroon Hingorani for advice on this in 2003. He named the Anderson 1991 paper (3) as one of the most relevant descriptions of the Framingham algorithm. The BNF charts were designed according to the 1<sup>st</sup> Report of the Joint British Societies (4) but this did not actually provide equation coefficients. Whichever risk equation were used, such coefficients would be required to programme the e-Nudge into the EMIS system. I then contacted Rupert Payne at Edinburgh University, who programmed the on-line CVD risk assessment algorithm that I myself use in practice and which includes both the BNF/JBS algorithm and various Framingham options such as CVD, CHD, and Cerebrovascular disease (<http://cvrisk.mvm.ed.ac.uk/calculator.htm>). He explained the broad issues around the programming of the risk charts and how he had translated the Framingham algorithm into a usable on line calculator based on these principles, which he agreed were not clearly evident in the literature.

In December 2005 the JBS2 report was published, a document that might have impacted on the e-Nudge design as it explained with greater clarity than previous sources exactly how these risk charts are constructed. The age bands (less than 50, 50-59, and over 60 years) were based on a calculation that assumed an age of 49, 59, or 69 years respectively. In addition, the Framingham algorithm that was used involves a summation of the CHD and cerebrovascular disease risk functions, but excluded heart failure and peripheral vascular disease outcomes in the risk estimate. The full CVD algorithm includes all of these.

It was not at all clear to me that this approach was appropriate, particularly in a research context where the age assumption might be difficult to defend. Essentially the BNF risk charts would give a 42 year old a risk estimate based on an age input of 49 years. In other words, the most accurate risk estimate available to the clinician is not the

one that is explained to the patient. I was careful not to allow my own personal opinion to dictate the choice of approach for e-Nudge, but I became aware through discussions with a number of others that they shared my view. Tom Marshall did not include the age assumption in his Sandwell project (5), nor in his other project published in the British Journal of General Practice in 2006 (6). Peter Brindle and Julia Hippisley-Cox were not using it for the QRISK project (7, 8). However, in the latter example they did define the Framingham algorithm as the summation of CHD and cerebrovascular disease risks rather than the full CVD equation, and if I were starting over again I would also have designed the e-Nudge using only these outcomes. In opting for the unmodified Framingham CVD algorithm I was also aware that should the e-Nudge prove in the trial to be an effective intervention, I would need to be able to describe its structure in detail to academics or clinicians anywhere in the world. These would include those from countries outside the UK who might not consider the JBS age adjustments appropriate in their setting.

By the New Year 2006 it was becoming late anyway to make significant changes, particularly as the Ethics committee had already approved the trial protocol. At this stage I was hoping to install the e-Nudge into the participating practices within a few weeks, and this could only follow successful performance testing of the software as described below. March 31<sup>st</sup> 2006 would mark the end of the second QOF year, making it unlikely that the trial practices would in fact be ready to engage until the late spring, but I wanted to be ready to go ahead in early April. The earliest practices actually commenced on June 6<sup>th</sup> 2006.

### **8.2.3 Programming the e-Nudge software**

The e-Nudge software was programmed for EMIS LV during early 2006. This work had followed my initial meetings with Newchurch during 2004/05 using their South Warwickshire data warehouse hosted in Teddington, described in Chapter 5. At the time of the August 2005 Ethics application, I was still expecting Newchurch to provide the

trial platform, but as discussed in Chapter 5, this proved not to be possible. The final phase of the e-Nudge design was consolidated at a meeting in EMIS's Rawdon, Leeds head quarters on 20.3.06 with David Stables. During this meeting a number of issues were clarified including the definition (based on electronic data) of a non-smoker, an issue that I had also discussed with Newchurch.

My tasks following this meeting were to send David Stables the equations and co-efficients of the Anderson Framingham algorithm, together with some examples for testing following his programming. We planned to install the e-Nudge into the test practice (Kenyon Medical Centres, Coventry) on 1<sup>st</sup> May 2006. Further discussions were carried out by email and telephone and included EMIS's Clinical Design Director, Shaun O'Hanlon. All three of us were trained as general practitioners, increasing our ability to identify important practical issues related to the process of identifying CVD risk at the point of care.

The equation co-efficients are given in the Appendix. I invented some case examples for CVD risk calculations and personally tested them using our Framingham equation. These were effectively 'back of an envelope' calculations and required no computer software other than a pocket calculator, but each step was recorded in detail in the field notes. The purpose of this exercise was to check that the algorithm that we intended to programme into EMIS as the e-Nudge would faithfully reproduce the estimates available elsewhere. Having calculated the risk level for each case based on the four component equations of the Framingham algorithm (see Figure 8.1 below), I then used Rupert Payne's Edinburgh University risk calculator on the same examples.

$$\begin{aligned}\mu &= \sum \beta_i x_i \\ \sigma &= \exp(\theta_0 + \theta_1 \mu) \\ u &= (\ln(t) - \mu) / \sigma \\ p &= 1 - \exp(-\exp(u))\end{aligned}$$

*Figure 8.1: Four components of the Anderson 1991 Framingham algorithm (3)*

**Example 1:** Male, aged 55 years, no diabetes, non-smoker, total cholesterol 5.2 mmol/L, HDL 1.2 mmol/L, systolic blood pressure 142 mmHg, no left ventricular hypertrophy (LVH).

**e-Nudge calculation** (from my field notes):

$$\begin{aligned}\mu &= 18.8144 - (7.391) - (6.9540) - (0.7904) \\ &= 3.679\end{aligned}$$

$$\begin{aligned}\sigma &= \exp(0.6536 - 0.2402 \times 3.679) \\ &= \exp(-0.23009) \\ &= 0.79446\end{aligned}$$

$$\begin{aligned}u &= 2.3026 - 3.679 / 0.70446 \\ &= -1.7325\end{aligned}$$

$$\begin{aligned}p &= 1 - \exp(-\exp(u)) \\ &= 1 - \exp(-0.1768) \\ &= 1 - 0.838\end{aligned}$$

$$= \mathbf{16.2\%} \text{ (probability of a CVD event over 10 years)}$$

**CVD Framingham score** (from <http://cvrisk.mvm.ed.ac.uk/calculator.htm>): **16.2%**

Using the same process on other examples (without showing the working from the field notes):

**Example 2:** Male, aged 55 years, no diabetes, smoker, total cholesterol 5.2 mmol/L, HDL 1.2 mmol/L, systolic blood pressure 142 mmHg, no LVH (i.e. same as Example 1 but a smoker).

**e-Nudge calculation:** 27.6%

**CVD Framingham score:** 27.6%

**Example 3:** Female, aged 51 years, with diabetes, smoker, total cholesterol 6.2 mmol/L, HDL 1.2 mmol/L, systolic blood pressure 138 mmHg, no LVH.

**e-Nudge calculation** 33.1%

**CVD Framingham score:** 33.1%

**Example 4:** Female aged 62 with diabetes, smoker, total cholesterol 5.0 HDL 1.5, systolic blood pressure 162 mmHg, LVH present.

**e-Nudge calculation:** 55.7%

**CVD Framingham score:** 55.8%

(I considered it safe to assume that this discrepancy was due to rounding up errors.)

**Example 5:** Female, aged 50 years, non-smoker, no diabetes, total cholesterol 6.8 mmol/L, HDL 2.0 mmol/L, systolic blood pressure 140 mmHg, no LVH.

**e-Nudge calculation:** 6.1%

**CVD Framingham score: 6.1%**

To clarify, we were not intending ever to calculate the CVD risk of a person known to have diabetes, but the diabetes input was required for e-Nudge because for Group 2/B (those with incomplete data but potentially at high CVD risk) it uses positive diabetes status as an ‘assumed value’ for anyone with no blood glucose on record for the past three years (and in whom it therefore might be unsafe to rely on their absence from the diabetes register). The Edinburgh on-line algorithm now no longer requests diabetes status as an input, but at the time that these field notes were recorded it continued to do so, facilitating our ability to test the e-Nudge against what I considered to be a ‘gold standard’ tool.

These five examples (and a number of others that I tested but did not record in field notes) made me confident that the algorithm we planned to use for e-Nudge was effectively reproducing the Edinburgh Framingham CVD risk calculation. We had tested it in both sexes, with a range of cholesterol and blood pressure values, and in the presence and absence of both diabetes and of left ventricular hypertrophy. Even though five is not a large sample, this testing process should have detected any discrepancy, as errors in co-efficient values or equation structure would almost certainly have been amplified during what was a fairly complicated, non-linear computation.

#### **8.2.4 Randomisation mechanism**

The e-Nudge was programmed to randomise automatically patients on the basis of the last digit of their ten digit NHS numbers. This number does not change, and is permanently available in the record as soon as the patient registers with the practice (or very shortly after). We considered the alternative used in other studies (9) of using the computer record number as the basis for randomisation. However, in UK practice these numbers tend to be allocated sequentially (i.e. in numerical order) as patients register.

This means that two patients registering on the same occasion (such as a married couple) would have almost inevitably received adjacent numbers. Because adjacent numbers are always different in their odd/even allocation, married couples would have tended consistently to be allocated to different treatment arms. Randomisation by NHS number overcomes this as the last digit is derived using the Modulus 11 algorithm (10) and there is no such tendency. However, despite the fact that my NHS number approach was more random than the computer number approach, the trial might still be termed ‘quasi-randomised’ rather than truly randomised, according to the definition used by Shojania et al (11).

## **8.3 Troubleshooting the software**

### **8.3.1 Performance testing the software ‘live’ in the test practice**

The next stage was for David Stables to programme this algorithm into EMIS LV along with the other components of the overall e-Nudge algorithm and install it into the test practice, which he did to schedule, and my first opportunity to investigate its performance in the test practice was on 5.5.06.

It was by no means obvious that the success of our algorithm demonstrated in my field note calculations would automatically produce the same results when programmed in to a practice database. The challenge of achieving this transition is an important focus of this research, as it depends on the ability of the algorithm to draw on existing, routinely collected data to support automated risk calculations. Many different issues are involved in this transition, most importantly the specific choices of risk factor Read codes used to feed into the algorithm. These were essentially selected by David Stables and were similar to the codes serving a similar CHD (not CVD) risk assessment tool already available in EMIS LV. We also discussed the choice of Read codes in some detail with Shaun O’Hanlon. My main role was to check whether our choices and



assumptions had succeeded in producing a workable CVD risk algorithm producing valid risk estimates for everyday UK primary care.

However, the testing stage of the e-Nudge programme explored more than this issue alone. I was interested not only in confirming that the programme would accurately identify those with a high Framingham risk score, but also in the likely impact of the software during routine practice, as this would determine its utility and acceptability for general practice teams.

During this testing phase (May 2006), I gained permission from the test practice to look at the lists generated by e-Nudge and the reminder messages that it triggered. At the time of this process I was working as a part time locum GP in the test practice. I had Ethics committee approval for the trial and the permission of the appropriate Caldicott guardians to ensure that the software was ‘fit for purpose’ to answer the questions addressed by the research. I also had the permission of the practice to investigate any problems identified.

The initial result of the e-Nudge applied to the test practice database on 5.5.06 is given in Table 8.1. The total practice population at this time (of all ages) was 11,086.

	<b>Over-50 pop<sup>n</sup></b>	<b>Group 1</b>	<b>Group 2</b>	<b>Group 3</b>	<b>Group 4</b>	<b>Group 5</b>	<b>Group 6</b>
<b>Int<sup>n</sup></b>	1737	203	541	131	10	1	69
<b>Control</b>	1685	233	456	123	4	0	67

*Table 8.1: Initial Group proportion results at the test practice on 5.5.06.*

Group 3 was the main group of interest, as these were the patients with sufficient risk factor data for a risk estimate and at identifiably raised CVD risk. This result produced a replication of the work that I had attempted remotely at Newchurch’s Teddington database, as described in Chapter 5. But it felt much more real, because the patients involved were identifiable within the practice and, provided they were in the intervention arm, reminder messages would appear on the screen whenever their notes

were opened. This provided the potential for feedback that I had sought in designing the trial.

My next task was to investigate the impact that the identified individuals (and their screen alerts) might have on everyday practice. To do this, I needed to find out what proportion of patients seen in clinics on that day (and on subsequent days of testing) would have generated e-Nudge reminders, and of which type. This would give an indication over whether the intervention would be sufficiently 'high profile' to be noticed by health professionals in the everyday working environment. It might have been the case, for instance, that the people identified were all 'hard to reach' or housebound patients who were rarely seen in the practice to have their notes accessed. If so, the e-Nudge would probably be too inconspicuous to make an impact on practice activity. At the other extreme, if e-Nudge alerts were likely to be triggered for the majority of patients seen during an everyday clinic, the practitioners might (at best) tire of it and become less responsive to the reminders. At worst, they might conclude that involvement in the e-Nudge trial was too disruptive to everyday workflow and decide to withdraw. Even during May 2006, with software installation planned in the very near future, the opportunity remained to tune the e-Nudge parameters if either extreme had become apparent during this testing phase.

This question, explored through the testing of the software in Kenyon Medical Centres during May 2006, could not easily have been addressed without this field work. Even though the Framingham algorithm was well defined, its co-efficients confirmed and validated, and its structure programmed into the necessary clinical software, it was impossible to predict how many people would be identified during an average working day in current UK general practice. A rough estimate of the proportion of patients identifiable in each group had been gained through the Newchurch work, although the proportions differed considerably when compared to Table 8.1 above. But the question that could not be answered prior to the e-Nudge installation was the proportion of those

identified that would actually present during a routine practice session for a doctor, nurse, or other primary care professional.

This phase was not a formal research project in itself, although it could potentially have been developed into an interesting one. It involved just a small number of sample clinics in one particular practice during a fairly narrow time window. However, it gave me a rough idea of the likely everyday impact of the e-Nudge on a practice of this size. This information was extremely useful later during the spring and summer of 2006, as I recruited practices in four waves to join the e-Nudge trial, and was able to negotiate on the basis of the testing phase findings.

I examined a general practitioner's clinic on the first test day of 5.5.06. Twelve patients were seen during the clinic, of which ten were in the over 50 year range amenable to the e-Nudge intervention. Of these ten, five were identifiable by e-Nudge (two in Group 1, three in Group 2). However, only two of these five were intervention patients. Two reminders would have therefore arisen out of the twelve patients seen.

This result seemed acceptable, but of course represented only one clinic. As I tested other clinics I became aware that a high proportion of the reminders were from Group 2 (those potentially at risk but with incomplete data). I decided to look into Group 2 in more detail by accessing the list of all current Group 2 patients and finding out what factors were most important in determining their identification in this Group. Seven cases were selected from the e-Nudge lists, and the following results were found

Age	Sex	Missing data	Comments
67	M	TC, HDL	Smoker
68	M	HDL, Diabetes status	“Stopped smoking” 1.9.2003
62	M	SBP, TC, Diabetes status	Recent smoker
60	M	Diabetes status	?Ex-smoker. Ratio only 2.1
74	M	SBP, TC, Diabetes status	Smoker, Diabetes status makes no difference
63	M	TC, Diabetes status	Smoker
56	F	TC, Diabetes status	Smoker, Diabetes status makes all the difference

*Table 8.2: Characteristics of a sample of Group 2 individuals identified on 5.5.06*

This sample was representative of an overall impression that I was gaining from testing the software. This was that the Diabetes status assumption in Group 2 was making a large difference to the size of this Group. It was at least partly involved in the identification of all but the first of this sample. In only one case would the person still have been identified had the Diabetes status been clearly negative (through a recent blood glucose value and absence from the diabetes register). This was a 74 year old male smoker. In the case of the 56 year old female smoker, this assumption made all the difference over whether or not she was identified, and the same applied to numerous other cases that I found.

Table 8.1 above suggested that about 1000 patients out of a total list of 11,000 would be identified within Group 2. All of these 1000 would be over 50 and therefore above averagely likely to be dealt with during regular care, although it could be argued that the patients with missing data might be those with less regular contact with the practice. I therefore expected that between 1/10 and 1/5 of patients presenting to the practice would be identified in Group 2 on an average day. This sort of figure seemed roughly supported by the GP clinic samples I had examined. I was interested to know what impact the removal of this diabetes assumption would have, in order to make a

final decision over whether or not it should be included. I therefore contacted David Stables and arranged for the Diabetes status assumption to be removed from e-Nudge on a trial basis. Following this change, patients would be assumed to not have diabetes if they were not on the Diabetes register, even if they had no recent blood glucose level to support this assumption.

In addition to this change, a number of other issues required action, to correct problems including coding issues that I identified. These were brought to light by the systematic checking of samples of patients listed in Groups 2, 3 and 4. From my field notes of 5.5.06, the following corrections were required:

1. A Group 3 patient was discovered whose alert indicated that the total cholesterol (TC)/HDL cholesterol ratio was 6.60. However, when I checked the record the most recent TC was 5.7 mmol/L (using Read code 44PJ), and HDL 1.0 mmol/L. A previous TC value was 6.6 mmol/L (using Read code 44P), and this was apparently the value that e-Nudge was using. It became clear (after discovering two other examples that I noted) that the e-Nudge was ignoring total cholesterol values recorded using 44PJ, and this required action.
2. There were one or two examples of deceased patients inappropriately identified by e-Nudge.
3. Clarification was required over the recognition of smoking status, brought to light by two patients identified in Group 2.

I spoke to David Stables from the test practice and he was able to remove the Diabetes status assumption more or less immediately, on a trial basis. I recorded receipt of a text message from him later the same day:

“153 intervention 126 control Group 2”

He also took action on the other issues identified. I then revisited the practice on 9.5.06 and found that as a result of these changes, other Group numbers had also changed (as well as Group 2). This was probably largely in response to the more effective detection of cholesterol levels through inclusion of Read code 44PJ, which reduced the numbers identified in Group 1 in particular. These were the patients with CVD who were out of the QOF targets for cholesterol or blood pressure. This change had also (predictably) increased the numbers identifiable with complete risk factor profiles and identifiable at risk (Group 3). Groups 4 and 5, identifiable only through blood glucose or blood pressure codes, were unchanged.

As expected, Group 2 had diminished significantly through removal of the Diabetes status assumption (and also to some extent through improved cholesterol value detection). Table 8.3 gives the new numbers identified in all the Groups, for comparison with Table 8.2 above.

	<b>Over-50 year pop<sup>n</sup></b>	<b>Group 1</b>	<b>Group 2</b>	<b>Group 3</b>	<b>Group 4</b>	<b>Group 5</b>	<b>Group 6</b>
<b>Int<sup>n</sup></b>	1737	92	153	166	10	1	55
<b>Control</b>	1685	119	126	149	4	0	50

*Table 8.3: Numbers identified in the test practice on 9.5.06. This followed temporary removal of the Diabetes status assumption for defining Group 2 and correction of a number of software problems.*

The overall numbers identified in Group 2 were clearly lower, but the difference that this would make to everyday practice needed looking into. I therefore carried out the same exercise as discussed above, by examining four routine practice surgeries, three by a GP, and one from a practice nurse.

### **Clinic 1 (GP)**

Twelve patients seen

Just one less than 50 (i.e. out of e-Nudge age range)

One Group 1 reminder

One Group 2 reminder (Systolic BP and cholesterol data missing)

One Group 3 reminder (71 year old male non-smoker SBP 124 TC/HDL ratio 4.33)

### **Clinic 2 (GP)**

Eighteen patients seen

Six less than 50 (i.e. out of e-Nudge age range)

Two Group 2 reminders only (One had just TC missing, the other both TC and HDL missing)

### **Clinic 3 (GP)**

Seventeen patients seen

Twelve less than 50 (out of e-Nudge age range)

No e-Nudge reminders at all

### **Clinic 4 (Practice nurse)**

Fourteen patients seen

Five less than 50 years (out of e-Nudge age range)

Three Group 1 reminders

This survey suggested that the profile of the e-Nudge had become significantly reduced as a result of the changes, most important of which was the removal of the Diabetes status assumption for Group 2. By the time the e-Nudge trial began (and during this testing phase), Group 1 had been effectively removed, as screen reminders to support the QOF had become commonplace and it was therefore no longer possible to withhold such reminders from control patients (see below). Based on this sample of four clinics, it appeared that the e-Nudge would only be active in a total of four out of 61 consultations. This seemed too inconspicuous an intervention to be expected to impact on processes of care. Largely for this reason (but also because I was becoming

particularly interested in the identification of patient groups most likely to benefit from testing for diabetes), we decided to reinstate the Diabetes status assumption for Group 2.

### 8.3.2 Recording of fasting blood glucose results

A further issue became apparent at this stage that I had not recognised before. This was that for Coventry practices (served by the clinical chemistry laboratory at University Hospitals Coventry and Warwickshire, UHCW), the vast proportion of blood glucose measurements were reported using the Read code 'Serum Glucose level' (44f), and very few using the code 'Plasma fasting glucose' (44g1). Despite the fact that this practice commonly requested blood glucose measurements on fasting samples, and using fluoride samples, the laboratory chose to use this code for reporting. It was this code that would therefore be placed in the patient's electronic record. The Warwick Hospital laboratory serving South Warwickshire practices also used the same policy of avoiding the Fasting plasma glucose code, but at least used plasma or blood glucose rather than serum codes in the reports. I carried out a search in the test practice on 9.5.06 for all patients whose record contained the two codes recorded from 1.1.04 to 1.1.06. The result is given in Table 8.4 and made me aware of how rarely the Fasting code was used.

Read code	Description	Number identified
44g1	Plasma fasting glucose	4
44f	Serum Glucose level	1514

*Table 8.4: Numbers of patients at the test practice identified with two Read codes present in their record between 1.1.04 and 1.1.06. The practice lists size was 11,086.*

I discovered later through discussions with both the laboratories of UHCW and of Warwick Hospital that a reason for this was that they do not like to assume that the blood glucose sample was definitely fasting. It is not uncommon for patients to present to a phlebotomist for a fasting blood glucose measurement having forgotten the



instruction to omit breakfast. In such cases, a blood glucose level between 7.0 and 11.0mmol/L might be interpreted incorrectly as indicating diabetes if reported using a fasting code. If they report it using a random or non-specific code then the clinician can decide how to interpret it by confirming with the patient whether the sample was truly fasting or not. This provided an interesting reminder to me that even in the case of machine operated blood testing and computer generated reporting by laboratories, followed by automated electronic transmission of results to practice records, valid concerns and opinions of essentially human origin may influence processes and outcomes of care. Primary care is a complex environment, but here was an influential perspective coming from a completely unexpected direction. Whether the potential barrier to the early detection of diabetes resulting from this stance is justified is unclear, but is perhaps worth exploring in a future project.

The follow up of borderline blood glucose values became an interest as a result of the e-Nudge experience and I was later invited by the British Medical Journal to co-author a 'Ten minute consultation' piece on the issues surrounding it. The lack of clarity over whether a sample was truly fasting or not was mentioned in the published article (12), as it is an issue of some importance to the creation of high quality diabetes registers in primary care.

The other issue brought to light by the discovery of relatively few fasting codes was that the identification of patients in Group 5 would require some work by the practices. I had already recognised this issue, but had not realised quite how rarely laboratories actually used the Fasting code. Group 5 identified patients with possible undiagnosed diabetes based upon:

Random glucose  $\geq$  11.1mmol/L OR Fasting glucose  $\geq$  7.0mmol/L anywhere in the record

AND

No *subsequent* Fasting glucose level  $<$ 7.0mmol/L OR 'Normal OGTT' code

A patient with a raised blood glucose value in the diagnostic range would therefore continue to trigger a Group 5 alert unless a new value at a later date was added that gave the fasting level as less than the diagnostic threshold for diabetes. Given that fasting samples taken to clarify diabetes status in such individuals would usually be reported by the laboratory using a random or non-specific code, this meant that to stop the Group 5 alerts from inappropriately appearing, the practice would need to insert the fasting level, properly coded by manual data entry rather than relying on electronic laboratory links. This was unfortunate, as it meant that e-Nudge could not be an entirely automated tool, but in practice the number of Group 5 individuals identified in each practice was very small. Nevertheless, the action required by practices to ‘manage’ their Group 5 lists and avoid unnecessary reminders was described clearly in an ‘e-Nudge User’s Guide,’ which I emailed to all practices as well as sending a hard copy (see Appendix).

In fact, Group 5 was soon withdrawn from the e-Nudge trial. The tool that replaced it, resulting from the subsequent QRESEARCH project described below, uses a simpler search protocol. It specifically accounts for this limitation in UK blood glucose data reporting.

### **8.3.3 Estimating the task of outcome data retrieval**

During the troubleshooting phase I took the opportunity to estimate the work required to retrieve the primary outcome data, i.e. identifying individuals experiencing CVD events during the trial, and counting/validating the overall number of events in each of the trial arms. The trial protocol (which was in fact published in April 2006, before the software was actually available for testing) stated that most CVD events would be identified by simple searches on practice registers, but that two groups of patient would be examined in more detail to confirm the number of truly new events. The first of these groups was those who had recently registered with the practice (who might have a

code for e.g. Myocardial infarction applied at a first consultation, even though the event had in fact occurred several years before). Such recording may occur whilst the patient's notes are awaited from the previous practice and the exact date is not yet known. The other group were those with a record of more than one event recorded during the trial. CVD events are quite often recorded more than once. For instance, in the case of a person experiencing acute myocardial infarction (AMI) as a first manifestation of ischaemic heart disease (IHD), both a code for AMI and a less specific IHD code might be applied, when in fact the patient has only had one event.

The first of these groups was quite straight forward, as the date range for identifying events simply needed adjusting. For the second group however, it became evident that the EMIS LV search engine would not easily identify people on the basis of having experienced more than one event. This is because the usual approach to practice searches is to identify groups of individuals sharing certain characteristics (such as at least one event), rather than identifying the events themselves. It became evident that in order to accurately measure the number of events occurring during the trial, every patient with any number of events would need to be examined and the number confirmed.

To get an idea of the numbers and the task involved in checking them all, I ran a search at the test practice on 9.5.06. This identified any individual who had AMI, a stroke (CVA), or transient ischaemic attack (TIA) over the three years 1.1.03 to 1.1.06.

118 patients were initially identified

Two of these were Temporary residents and so not counted, leaving 116

One had had a record of 'Vertebrobasilar insufficiency' which is not considered a relevant CVD event (see Chapter 2)

This left 115 patients with at least one cardiovascular event out of a background practice population of 11,086.

AMIs:	42
Strokes:	40
TIAAs:	37

Two patients had had both one AMI and one TIA

Two patients had had one CVA and one TIA

One patient had had two CVAs

One patient had had two TIAs

I therefore recorded 119 events occurring in 115 individuals. 109 had one event, and six had two events. I found no examples of more than two events in the same individual in this survey.

The overall estimated event rate for AMI, CVA and TIA, based on these figures was therefore approximately 358 per 100,000 patient years. This exercise aimed to estimate the number of AMIs, CVAs and TIAs occurring more than once in the same individual. It did not include new diagnoses of IHD without AMI (eg onset of angina). These would have brought the estimated event rate closer to the predicted value of 1206 per 100,000 patient years used in the power calculation and based on published estimates. However it confirmed that despite our original hopes that the primary outcome measure could be extracted largely through electronic searches, an examination of every event recorded during the study would be required to derive an accurate figure.

#### **8.4 Issues affecting recruitment**

I aimed to recruit up to twenty-six general practices in Coventry and Warwickshire to participate in the trial. This figure was based on the total number of practices connected

with the Newchurch database. At the initial stage (including the time when Ethical approval was gained in August 2005) I expected that Newchurch would be instrumental in the e-Nudge project and this was the maximum number available, all of them within South Warwickshire, even if we included all software providers.

After EMIS took over as the platform provider for the trial software, this approved number remained my target, but I was then able to recruit over a much wider area, including Coventry, Rugby and North Warwickshire. The availability of EMIS practices (of which 80% ran the LV version for which the e-Nudge was programmed) meant that practice numbers were not a problem. NHS Research and Development approval was however, delayed particularly for North Warwickshire Primary Care Trust (PCT), almost to the point of excluding this PCT due to the time pressure to commence the trial. However we recognised the importance of including an above averagely deprived area in which coronary heart disease standardised mortality ratios were known to be particularly high.

By the time we were ready to test the e-Nudge software in the test practice (Kenyon Medical Centres) my attempts to recruit practices were well underway. In retrospect, I look back with some anxiety at my confidence in moving this recruitment process forward before the e-Nudge software had been finalised and tested. However, from the start of recruitment I knew that EMIS would support the trial, and this made a huge difference to practice receptiveness.

An interesting field note that I made on the 14.4.06:

*Invitation letters sent out to further practices working through the list on the Excel sheet 'EMIS LV practices in Coventry'. Stopped at No. 30 as we may have enough Coventry practices, and to make room for IPCRESS.*

IPCRESS is an ongoing multi-centre study of an on-line cognitive behavioural therapy intervention for depression, for which the University of Warwick was actively

recruiting around that time. As Research Practice Lead for Warwick-Coventry Primary Care Research (WC-PCR) I was involved in this recruitment drive. This field note reminds me of the competing priorities that my own research was exposed to and my responsibility in the Medical School to assist with recruitment for primary care studies in general.

The total number of patients required for the primary outcome was 70,000. Unfortunately, as discussed in the previous chapter this was initially believed to be the total population sample figure but after a revision to the calculation I required the same number over 50 years. Resources were limited and I stopped at 19 practices, providing approximately 38,000 over 50 years. Limiting factors included my own time, and that of the Research Nurse Rachel Potter, who became involved with a number of other projects during this time. Increasing the number of practices by a factor of nearly two would have substantially changed the scale of the endeavour and would have required both Ethics Committee and R&D re-approvals, as I only had permission to recruit a maximum of 26 practices.

However, I was confident that whilst we might be under-powered to demonstrate a reduction in the primary outcome (cardiovascular events), we had a very ample number through which to demonstrate changes to processes of care which, as was becoming evident in the literature review, would probably be more likely to be influenced by a reminder intervention.

## **8.5 Problems occurring during the trial**

The first problem occurring during the trial was the result of an initial data capture problem at baseline. The outcomes of the trial were the annual CVD event rate over two years and the proportions identified in each of the Groups at the end of the trial. They did not therefore depend upon the baseline data. However, I was keen to record these data for two reasons. Firstly, to demonstrate the success of randomisation and secondly,

to publish the baseline proportions as a reflection of the adequacy of UK primary care data to support CVD risk assessment. This publication (13) was delayed significantly as all of the searches needed to be re-run by EMIS back dated to the start date in each practice.

During this process, a more specific data capture problem occurred in one of the 19 practices, for no reason that came to light. This was not actually evident until much later, when the original figures for the background denominator population (i.e. those over 50 years) from this practice were seen to be low compared to subsequent figures. The difference was too large to be attributable to new practice registrations. It was possible to retrieve accurate figures from 25 days after the installation of the e-Nudge at this site, but not before this. This did not (as discussed above) affect the trial outcomes but it was mentioned in the final published trial report (14).

Meanwhile, the e-Nudge continued to operate successfully, in every respect other than the identification of Group 5, those with possible undiagnosed diabetes. The algorithm for identifying this group was clearly malfunctioning (based on examples arising in the trial practices). Through discussions with a GP who spotted the problem and EMIS, we were able to correct this problem quickly, but soon after this the Group 5 was withdrawn from the trial for reasons discussed in the following section.

## **8.6 Changes to the protocol after commencing the trial**

### **8.6.1 Shortening of the e-Nudge reminder messages**

After nine months I arranged for a shortening of the e-Nudge reminder messages. Originally these were designed to provide a clear justification for the identification of an individual in whichever Group was involved. However, it became apparent that (as discussed in Chapter 6) the messages were unnecessarily wordy and, particularly in the cases of practices using the reminder format that appears at the bottom right corner of

the screen, they were potentially obstructing other information during the consultation. This format appears spontaneously and remains visible during the consultation unless actively removed by a mouse click, whilst the centrally appearing format requires an obligatory keystroke to remove it, after which it is no longer visible unless actively called up again. Practitioners using the first type were not used to having to clear reminders from the screen at all, as they were generally small enough to allow visibility of the other screen information, and their persistence during the consultation may be a positive feature. The original e-Nudge messages however were relatively obstructive and would make removal by key-stroke essential. This created problems for the one practice that withdrew after less than 6 months, and another practice discussed withdrawing with me for the same reason. In fact, this latter practice (and another) also mentioned the effect of the lengthy messages on reception staff, which made me aware that the e-Nudge was affecting workflow generally in the practices and not just the clinicians. However this practice agreed to remain in the trial once the messages had been shortened.

### **8.6.2 Withdrawal of Group 1**

Group 1 represented those with established cardiovascular disease or diabetes who were out of the QOF target for blood pressure or cholesterol levels. During 2004 (the first QOF year) and into 2005, screen reminders were not routinely used by all practices to support QOF targets. Including this group in e-Nudge was expected to make involvement in the trial more attractive to practices, as the software would help them identify patients who required action and might therefore improve their payments. However, by the end of 2005 (and after the Ethics committee application) it became evident that QOF reminders had become 'usual practice'. It was still an option to switch them off, but few practices were likely to take this option, as their QOF performance might suffer. By the time EMIS were making the final adjustments to e-Nudge in May 2006, it was clear that to withhold QOF reminders from control patients would mean



depriving them of an important part of ‘usual care.’ The decision was therefore taken to remove the e-Nudge Group 1 screen reminders. In principle the list of identified patients was still available (for intervention patients), but the flagging mechanism had been removed.

### **8.6.3 Withdrawal of Group 5**

Group 5 identified individuals with possible undiagnosed diabetes, based on past blood glucose values in the record. In the baseline data (following the re-run as described above) there were 33 such individuals identified in both arms of all the trial practices combined. The original idea of including this group was essentially to support the quality of the practice diabetes registers, to ensure that the e-Nudge did not conduct a CVD risk estimate on someone known to have diabetes. Such an individual might be under treatment for diabetes but for some reason not be on the diabetes register, in which case it might assist practices to have this pointed out. This number was not great, but it was sufficient to make us question the ethics of not acting upon those in the control arm, as they would not be flagged up to the practice teams. Their names would be listed in the practice servers but inaccessible to practice team members for control patients.

The e-Nudge software could identify these individuals, but it could not tell us how many of them had truly been ‘missed’ from those whose raised blood glucose value was in fact measured the week before and who were planning to be reviewed in the near future to discuss the results. In such cases their identification would create no ethical issue and no intervention into the usual process of care would be required.

The existence of such identified patients was discussed in my meeting with David Stables on 20.3.06. At that stage it was unclear how many were likely to be identified in e-Nudge, and whether this might present an ethical issue. One of the unknowns was over whether individuals identified in Group 5 had actually had their raised blood glucose measurement ‘missed’ or whether in fact it was already in the

process of follow up. To clarify the situation, David Stables and I approached Julia Hippisley-Cox at the QRESEARCH database in the University of Nottingham.

## **8.7 The QRESEARCH survey**

The QRESEARCH database contains anonymised data from over 500 EMIS practices all over the UK. We designed a new project to estimate the number of people registered with general practice with biochemical evidence of undiagnosed diabetes, using a similar (but modified) approach to e-Nudge. The research question was developed into a cross-sectional survey protocol. This was approved by the QRESEARCH Scientific Advisory Committee and was covered (as are all QRESEARCH projects) by Trent Multiple Research Ethics Committee. This survey was undertaken in June 2006, and involved the application of a modified version of the e-Nudge Group 5 search on the QRESEARCH database. David Stables, Julia Hippisley-Cox and I were joined on this project by Shaun O'Hanlon (EMIS Clinical Design Director) and Azeem Majeed (Professor of Primary Care at Imperial College, London). This was a collaborative project and I present an outline of the survey here as a secondary output of the research and not primary data for this thesis. A more detailed description is given in the final published report included in the Appendix (15).

### **8.7.1 Survey sample**

A total of 480 practices over the UK met the eligibility criteria for inclusion in the survey, (complete data transmission to QRESEARCH to 1<sup>st</sup> June 2006). This provided 3,630,296 records of patients registered on that date. QRESEARCH has been validated against other sources to be representative of the UK population registered with general practice (16).

### **8.7.2 Search strategies**

We decided to simplify the search protocol used in e-Nudge as we recognised that it was unnecessarily complicated and, as discussed above, it relied on uncertain fasting/random blood glucose coding that was potentially resolvable at the practice level but not through QRESEARCH. We chose the following search criteria on patients of all ages with no diagnosis of diabetes and no history of impaired glucose tolerance:

**Strategy A:** Patient identified if the most recent blood glucose measurement is either a fasting level of 7.0 mmol/L or higher, or a random level of 11.1 mmol/L or higher. If the code is non-specific then a random level is assumed.

**Strategy B:** Patient identified if the most recent measurement is 7.0 mmol/L or higher, regardless over whether the code was fasting, random, or non-specific.

### **8.7.3 Rationale for the search strategies**

In designing these strategies, we had in mind a new software module for use in clinical practice, that could run the same searches on a nightly basis, as for e-Nudge and for the QOF. EMIS had committed to develop and install such a module if significant numbers of patients were identified in the survey. We wished first of all to identify patients with definite biochemical evidence of undiagnosed diabetes (by using the diagnostic thresholds, Strategy A). Secondly, we wished to identify patients who justified follow up testing for a borderline or raised blood glucose. Strategy B in fact includes Strategy A, but also includes those with more modestly raised random readings. The recently published JBS2 guideline of December 2005 (17) recommended that during the process of cardiovascular risk estimation, random blood glucose values of 6.0 or higher should be followed with a fasting sample. If in such a case the fasting value were returned as less than 7.0mmol/L then diabetes was not evident (although the patient might have impaired glucose regulation), and such a patient would then no longer appear on the

Strategy B list if this were updated regularly through a software module. If the follow-up fasting level were greater than or equal to 7.0 mmol/L then the patient should be on the diabetes register, provided the diagnosis was considered sound on clinical grounds. Either way, they would be removed from the Strategy B group. This was the reason for selecting 7.0 rather than 6.0mmol/L as the threshold for this group. It produced an identifiable population with a clear, unmet health need.

The assumption concerning non-specific codes for Strategy A was a conservative one. Individuals with diabetes might be missed if a fasting measurement between 7.0 and 11.0mmol/L were reported by the laboratory using a random or non-specific code. This appeared to be happening in the local laboratories serving the e-Nudge practices (see Table 8.4 above).

The results of the QRESEARCH survey were published in the *British Journal of General Practice* in March 2008 (15). We found that out of the denominator population of 3,630,296, Strategy A identified 3758 patients (0.1%), whilst strategy B identified 32,785 (0.9%). We found that a third of the population over 40 years have a blood glucose measurement electronically recorded in the record, suggesting that this information is recorded commonly enough to be useful for such targeting. The survey also indicated that 15.9% of results nationally were reported using a definitely fasting code, 22% definitely random, but in 62% a non-specific code was used. A number of the non-specific codes may have been reported on samples that were actually fasting.

This project was able to answer a question that the e-Nudge data could not. How long ago was the blood glucose measurement leading to a patient's identification in a search made, and how was this distributed over the identified population? Were the people requiring follow-up of borderline or raised levels in fact those whose test had been carried out very recently and for whom no additional action was required? This outcome was included in the published paper, and suggested that over a third of strategy A patients and over half of the Strategy B patients the blood glucose measurement that required follow up was taken over a year ago. In addition, we found that 440 out of the

480 practices surveyed had at least one Strategy A patient, and all but one had at least one Strategy B patient.

Projecting the figures to the UK population, around 60,000 patients might be identified through Strategy A, and 528,000 through Strategy B (18). This might therefore make a substantial impact on the problem of undiagnosed or late-diagnosed diabetes, provided that the identification of such individuals could be linked to practice based processes of care, both opportunistically (at the point of care) and systematically (through the availability of lists in practice systems).

The result of this project was that a new software module was designed and installed into all EMIS practices throughout the UK to run the Strategy A and B searches every 24 hours. This was a major output of this research and is discussed in Chapter 10. The module was initially installed by an EMIS patch transfer around October 2006 as an optional facility to assist practices in identifying such patients. At this point we decided that it was no longer appropriate to keep Group 5 in the e-Nudge trial and I wrote to all practices to inform them of this change and to draw their attention to the existence of the new EMIS module which they could access if they wished. I also applied to the Ethics committee for a substantial amendment to the protocol, which was approved. However, given the scale of the problem EMIS considered this to be a safety issue and around April 2007 the lists of identified individuals became linked non-optionally to screen alert messages to highlight the previously raised blood glucose value. The reminder message is in the same format as QOF alerts and states: "RULE OUT DIABETES, LATEST GLUCOSE HIGH."

## **8.8 Collecting the trial results**

The collection of CVD event data was conducted at the end of the trial (and after the first year for the purposes of data monitoring). The Standard Operating Procedure for collecting the primary outcome is given in the Appendix. One of the advantages of the

e-Nudge software design was its ability to automatically store the Group data every eight weeks in the practices' servers (for the secondary outcomes). However, a number of problems arose during the final collation process. These were instructive, not only for this project, but perhaps in a more general way given the increasing tendency for primary care research to depend on electronically coded outcome data.

### **8.8.1 Access to the Bureau system server**

Three of the e-Nudge practices were linked to a 'Bureau' system hosted by Coventry Primary Care Trust (PCT) that included a total of ten EMIS LV sites. For these practices, a shared server supported administrative data and, importantly for the trial, this server was the destination for the 8-weekly e-Nudge outcome data retrievals. During the summer of 2008, around the time when the outcome data were ready to be collected, a disruption occurred, limiting access to this server for these practices for several weeks. This did not affect the use of the practices' clinical software, and the e-Nudge alert messages still operated, but it did mean that documents stored in the Bureau system were temporarily unavailable. This included the automatically stored figures for the numbers of people identified in each e-Nudge Group. I initially contacted Coventry PCT to overcome this problem, and visited their technicians to attempt to resolve it within the Bureau system at the PCT offices. However, it was only by contacting EMIS technicians based in Leeds that the documents were recovered. This problem did not affect the trial and no information was ultimately lost, but for a time I wondered whether important outcome data might be irretrievable. This highlighted the risk involved in embedding a research study within the NHS to the extent that essential outcome data were dependent upon routine care processes.

### **8.8.2 Distinguishing new cardiovascular events from follow up entries**

A problem evident early on in the first round of data collection (conducted by Research Nurse Rachel Potter for data monitoring after the first year) was the sheer scale of the

task, due it emerged to the inappropriate identification of codes for 'Review' of a vascular diagnosis, where a new event had not in fact been experienced. This problem was fortunately resolved by revising the search protocol slightly (through EMIS LV's Advanced Code Options) to only include 'First' or 'New' instances of the G3 or G6 code groups. G3... and G6... are the 'parents' of all lower level coronary artery and cerebrovascular disease codes respectively.

### **8.8.3 Home grown codes and unwanted G6 codes**

The problem of 'home grown' codes was discussed in Chapter 1. Clinical software systems allow practices to create their own codes to manage (usually administrative) issues within the practice. These codes may be very useful but their use is now generally discouraged as it is seen as an obstacle to data integration and interoperability above the practice level. In one South Warwickshire practice, a code named 'Cardiac diabetic' had been created and whilst this was not a 'child' of G3 or G6, it had been linked to the G3 group, and so was identified inappropriately in my search for cardiovascular outcomes. The linkage may have been through an unidentified template stored in the system but this was never discovered despite attempts by the practice manager.

The possibility of capturing patients inappropriately through codes that were linked to (rather than actually children of) the G3 and G6 codes had not occurred to me, so this was useful. It reinforced the need to check every single patient identified to confirm the number of truly new G3 or G6 coded events during the study. However, this did not solve the practical problem of completing data collection in practices where large numbers of patients were being identified inappropriately. Another such practice was based in Coventry, and in this case ten codes linked to G3 (including Cardiologist seen, Beta-blocker contra-indicated), and seven identified under G6 (including Basilar artery syndrome, Subclavian steal syndrome) were detected. This latter group included 'Vertebrobasilar insufficiency' which has the code G65-1, a child of G65 (Transient

cerebral ischaemia). I was aware (as discussed in Chapter 2) that this commonly used code would lead to the identification of patients who had not in fact had a true cardiovascular event in the commonly used sense of the term. Through liaison with the lead general practitioner for IT issues in this practice, we arranged for a slightly more detailed repeat search that excluded unwanted codes whilst retaining the identification of patients with appropriate codes. This reduced the number identified in this practice from over 600 to 58. A much smaller practice that was less computerised had just 16 patients identified, and I needed to examine the paper records of three of them. Three out of the sixteen had been coded with vertebrobasilar insufficiency (G65-3) and one with 'Drop attack' (G65-1), another example of a G6 code that does not usually signify a true cardiovascular event.

Despite the efforts made to exclude inappropriately identified individuals from the searches, I was careful not to miss any cardiovascular events, and the result was that 2121 electronic records were checked in the 19 practices to identify the 930 events.

## **8.9 Interviews with members of the public**

As part of a process evaluation (for which Ethics committee approval was gained), eight members of the public registered with an e-Nudge practice agreed to take part in 60 minute in-depth interviews concerning their beliefs and attitudes towards cardiovascular risk and prevention. The aim of this was to explore some of the human obstacles and enablers to CVD risk reduction that might impact on the e-Nudge trial. In the process I also gained an awareness of the importance of including a qualitative element to a clinical trial through involving appropriately trained colleagues, in the same way that I would involve statistical expertise as part of a complete research team. As this study was limited in scope it is included only in an appendix to the main thesis. It nevertheless gave me some insights into patient perspectives regarding cardiovascular risk reduction.



## **8.10 Clinician interviews**

Semi-structured interviews were conducted with a number of practice based staff (two general practitioners, two practice nurses and a practice manager), but these proved not to be useful. This was perhaps because I was the researcher leading the e-Nudge trial in which they were engaged, and opinions appeared to be biased in favour of the software and the e-Nudge approach in general. We had initially intended to conduct a total of 24 such interviews, but decided not to continue as the data were not sufficiently useful. Recruitment of a research fellow to continue the interviews on my behalf might have overcome this problem, but could not be resourced within the PhD budget.

The exception to this was an interview that I conducted with a GP who was particularly interested in CVD risk reduction. In contrast to the statements of health professionals in other practices who regarded the e-Nudge approach to be very proactive compared to what they were offering, he seemed to suggest that such action was a minimum standard and a basic responsibility of general practice teams.

## **8.11 Summary**

This thesis has relied very much on qualitative information as well as on the quantitative data generated in the e-Nudge trial. The field notes that I made prior to, during and after the trial have enabled me to place the findings in context and also to answer questions that the trial alone could not. Relevant issues included bureaucratic obstacles, resource limitations, unforeseeable developments causing slippage, dependency upon goodwill, acceptability of an intervention to clinicians and other staff, and the importance of patient perspectives. Some of these issues were lessons learnt the hard way through the process of my training and would be less likely to occur in future. But most are an inevitable consequence of conducting research in a setting of competing priorities and this perhaps applies to the majority of primary care research.

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## Chapter 9: Reflections on the completed research

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### 9.1 Introduction

This chapter provides some reflections on the practicalities of conducting primary care research at the end of this PhD project, on how I might have chosen to act differently if starting again, and on general lessons learnt at the completion of this thesis. The two main areas of research were the systematic review and the e-Nudge trial itself.

### 9.2 The systematic review

The systematic literature review was described in Chapter 4. This taught me a lot about evidence synthesis, the dangers of poor trial design, the value of a pre-published trial protocol, and the difficulties created for future researchers if interventions are not described in detail and results not reported clearly. A number of specific lessons would help me proceed differently in future. Difficulties with bibliographical software were resolved within the timescale of this project that initially were a significant barrier to progress but would not be a problem again. Whilst I chose a fairly comprehensive range of databases to include, if I were starting afresh I would apply a wider range of terms in the initial search. The requirement that our papers all included 'Reminder systems' as a term was one of the reasons for the lack of overlap with the Shojania 2009 and Kawamoto 2005 reviews as discussed in Chapter 4.

I learned a more general lesson about evidence synthesis through this work. This involved the use of *binary* outcome measures in the trialling of interventions. Binary outcomes are required to derive odds ratios or risk ratios. This is the basis for logistic regression and other models used to determine the relative influence of predictor variables as discussed in Chapter 2. In the systematic review, a distinction was made between studies using binary outcomes (subdivided into process outcomes and

clinical outcomes) and continuous outcomes such as length of hospital stay. Whilst RevMan software is designed to incorporate either binary or continuous outcomes, it is difficult to synthesise both at the same time, and binary outcomes seemed to be much easier to handle. Binary outcomes are the basis for measurements of absolute risk reduction, from which the *number needed to treat* is derived for the intervention.

In studies of cardiovascular disease, dichotomous outcomes seem particularly apt, because generally speaking important CVD events (e.g. myocardial infarction, stroke) have either ‘happened’ to an individual by a certain time point, or they have not. They are discrete events. The development of disease registers in primary care has emphasised (and perhaps amplified) this dichotomy: the recommended management of a patient for control of vascular risk depends very significantly on whether s/he is or is not on a vascular disease register. But in clinical practice we need to advise patients about all potential benefits and risks, and not all of these are as easily conceptualised in binary terms. Benefits of lipid lowering or blood pressure reduction might in theory, for instance, have a long term effect on cerebrovascular perfusion that is more appropriately measured using continuous measures of cognitive function. Similarly, adverse effects of such medication might include non-discrete outcomes such as reduction in quality of life that are less likely to be the primary outcome measure of randomised controlled trials. These are more likely to focus on the binary outcomes that may make different trials (often already heterogeneous in their specific interventions and settings) potentially comparable. So whilst I found binary outcomes much easier to handle than continuous outcomes in conducting the systematic review, their potential to over-simplify quite complex clinical phenomena concerned me a little as a clinician.

Even if we define CVD ‘events’ (such as myocardial infarction or stroke) as binary phenomena, *risk of a CVD event* is a continuously distributed variable. However there is a tendency to dichotomise this concept as well, in the quest for the ‘high risk’ population defined by an essentially arbitrary threshold of risk. Marteau and Kinmonth

discuss the implications of this tendency for the communication of risk to individuals considering CVD risk assessment as a screening procedure (1).

A further example where priorities may potentially conflict is in the use of composite endpoints, which increase the power of a study by providing more events than would occur for a single endpoint. The impact of the intervention may then be more visible and the result more likely to be significant. However, the individual outcomes within the composite endpoint may have quite separate importance and relevance to the patient (2), who ultimately needs to decide whether or not potential benefits of the intervention concerned are outweighed by potential adverse effects.

### **9.3 Realities of conducting primary care research**

The literature review was completed relatively late and I would have benefitted by conducting it earlier on during the preparatory phase of the e-Nudge trial. However there were good reasons for the delay.

Firstly, there was significant time pressure to develop the trial protocol, design the actual software (programmed by EMIS), and recruit the participating practices in order to generate the outcome data within the necessary timescale. Part of this pressure was the result of the PhD submission deadline, but part of it was due to developments in primary care that might make the trial impossible. The original e-Nudge ‘Group 1’ was withdrawn simply because screen reminder interventions became routine practice during 2005/6, making their absence from the trial’s control arm impossible (and perhaps unethical). I was aware that other developments might include the targeting of the population that I defined as e-Nudge Group 3 (Group A in the final report), the main group of interest. Had similar reminder interventions become routine then this would have jeopardised the entire trial. Whilst the targeting of primary prevention candidates has indeed become recommended through the UK vascular screening programme, the requirement to provide screen reminder interventions that would be expected by

practices if linked to remunerative payments (David Stables, personal communication), has not yet occurred. An important lesson from this related to the risk to research posed by an evolving clinical or organisational environment that may quickly make research questions either out of date or unanswerable. This particularly applies to research into areas of care that are topical, in which policy may alter rapidly.

Secondly, the focus of the research changed during the five year time course. It originated from my interest in pattern recognition in primary care data (an activity, however complex, that requires a *unidirectional* flow of information from database to investigator), but also included a broader interest in *feedback* (i.e. bidirectional flow) particularly within the consultation environment, with its potential for more unpredictable outcomes. This unpredictability includes the sometimes irrational (from a traditional biomedical perspective) decisions made by individuals who may have different priorities to the designers of clinical decision support systems. The sociological aspects of influencing practitioner and patient behaviour at the point of care became at least equally interesting as the pattern recognition aspects. This then refocused the research around consultation based reminder interventions. Any shift in the emphasis of a developing research programme makes the achievement of deadlines more difficult, even if projects within it are tightly time-managed.

#### **9.4 Design issues of the e-Nudge trial**

A number of issues and problems arose during the design of the e-Nudge trial. Some of these occurred during the preparatory phase and have been discussed earlier. Others arose after the trial was underway and led me to reflect on how I might have done things differently had I had the chance to start afresh.

#### **9.4.1 Clustering and contamination**

The first issue concerns the decision to randomise individually rather than by practice. This question was raised by two colleagues at the Warwick Medical School Clinical Trials Unit who commented on a draft trial protocol and pointed out the potential benefits of cluster randomisation. However they also recognised the finite recruitment capacity of local practices and the benefits of individual randomisation.

Individual randomisation within the practice runs the risk of contamination, through which the beneficial effects of the intervention may spill over into the control population. In the e-Nudge trial, a control patient might be more likely to have his or her cardiovascular risk factors recorded, controlled, or in other ways addressed if the clinician has recently been triggered to action by a reminder related to a similar intervention patient. The effects of the intervention may then be less evident because the difference between the care provided in each arm is reduced. An effective intervention might then produce a non-significant result. Whether contamination would be likely to occur for the e-Nudge intervention was discussed during the planning phase. For some parts of the e-Nudge, e.g. the group that identified individuals with CVD requiring a blood glucose measurement, there was significant risk of contamination, as the practitioners' awareness of the need to complete such data might be raised in a general way during the trial due to intervention alerts. However, for the more important Groups 3/A and 2/B, a risk estimate was required to identify the patient as justifying action, requiring a computation much less likely to occur in the mind of a clinician without the help of software or other such tool. McManus et al have demonstrated the limited ability of health care professionals to make such estimates without the help of risk calculation tools (3). The alerts resulting from this automated computation would not occur for control patients, and so contamination was less likely for these e-Nudge Groups. A further factor that led me to assume that contamination would not be a major problem was that (as mentioned in Chapter 4), the effects of reminder interventions on practitioner behaviour may decay quite rapidly when the



intervention is withdrawn (4). There is evidence that reminders that require an active initiative on the part of clinicians are more likely to influence practice than those appearing spontaneously (5). These effects might also reduce the chances that any impact of the e-Nudge would persist in future consultations with control patients. Finally, a study by Chambers et al (6) deliberately tested the effect of potential contamination. Physicians caring for patients requiring influenza vaccination were randomised into a group always reminded of this requirement at the point of care, those never reminded, and an intermediate group reminded only 50% of the time. The rate of vaccination in the intermediate group, on occasions when the reminder was absent, was lower than the rate in the group never reminded. This suggests that physicians who are sometimes reminded become dependent on the reminders, and that the effects of reminders do not persist in future consultations in which they are withheld.

Cluster randomisation at the practice level protects against contamination, but needs to be balanced against other issues. One of these is the inflation of sample size resulting from the 'design effect' due to clustering (7). This may make the necessary sample size prohibitive, depending on the intra-class correlation coefficient (8), which is often poorly quantified for the current study population and needs to be estimated from published values measured in comparable researched populations. Another negative aspect is the need to identify the important criteria for stratification in the randomisation of clusters. If these are not identified adequately, important differences may become evident between the trial arms that undermine the trial's internal validity. An example of this is the study by Mitchell et al (9), in which a failure to recognise training practice status as a basis for stratified randomisation was recognised by the authors as a possible weakness of the trial.

I concluded that individual randomisation was the most appropriate approach for the e-Nudge trial given the resources available, but a similar trial carried out on a much larger scale involving many more practices would lend itself better to a cluster randomised design.

#### **9.4.2 Choice of primary and secondary outcomes**

Whilst we named the CVD event rate as the primary outcome, the chances of actually influencing it over a two year timescale seemed very low given the high number needed to treat for CVD risk reduction interventions such as lipid lowering therapy in primary prevention settings, and I was more interested in the changes in group proportions, for which the trial was more than adequately powered. But as the CVD event rate seemed likely to be the most difficult outcome to change, and given (based on the existing literature, as discussed in Chapter 4) that hard clinical outcomes are generally more valued than changes in process measures, we considered that this was the most appropriate primary outcome. If we had called this a secondary outcome instead the trial would not appear to have been underpowered and non-significant in its primary result. If I were to repeat the e-Nudge trial with similar resources available I would consider either reversing the choice of primary and secondary outcomes, or stretching the trial resources to include more practices. An even better option would be to obtain sufficient funding for a larger trial more adequately powered to detect a reduction in CVD events.

#### **9.4.3 All events versus first events**

The chances of demonstrating an effect of an intervention under trial is improved if the ‘signal/noise’ ratio is maximised. This issue was emphasised at the *Randomised Controlled Trials* course that I attended at Oxford University in April 2006, after the e-Nudge trial design had been finalised. A missed opportunity to improve this ratio was to consider only *first* cardiovascular events in the primary outcome measure. The reason why I initially deemed this inappropriate was that as the trial went through the Ethics committee I was still including secondary prevention patients (those with existing CVD or diabetes with uncontrolled blood pressure or cholesterol) as the separate Group 1. As long as this group were included, it made sense to include all CVD events in the over

50 year age group occurring during the trial as the outcome. There were also secondary prevention patients identified in Group 4/D (patients over 75 with persistently raised blood pressure), in the original Group 5 (those with possible undiagnosed diabetes), and in Group 6/C (those with CVD but no recent blood glucose on record). When Groups 1 and 5 were withdrawn (for reasons discussed in Chapter 8) it was too late to revise the outcome measures as the trial had started. But the study had become a trial almost exclusively on the primary prevention population. Groups A and B (which were always the groups of greatest interest simply because they were the only ones requiring the Framingham computation) by definition did not include secondary prevention patients. Whilst the patients included in these groups changed during the study (and they therefore could not easily have been used as a denominator population for the trial outcome), I could have confined the CVD event outcome exclusively to the primary prevention population. This would have been easy to do using EMIS LV (the software platform used for the trial), as the outcome searches defined in the data collection SOP (see Appendix) could simply have identified 'First' events rather than 'First or New'. This change would have reduced the number of CVD events analysed (reducing the power) but confined them to a smaller, more relevant denominator population, improving the signal/noise ratio in the outcome analysis. As it stood, the e-Nudge trial outcomes still included events occurring in patients with established CVD at the start of the trial, who by definition could not have been exposed to the Group A or Group B reminders. These patients were experiencing CVD events for at least the second time, which had implications for the statistical analysis, which was based on the Poisson assumption that events were occurring randomly in the population. A much 'cleaner' outcome would have been the incidence of first events in those with no history of past events. This would actually have been easy to detect using the EMIS LV software, but the sample size would have needed to be significantly higher as it would have only involved the primary prevention population.

#### 9.4.4 Imputation of missing risk factor values

The final stages of the e-Nudge software design took place with considerable time pressure. One area that could have been improved was the issue of ‘missing data,’ i.e. the assumptions made for Group B patients whose risk profiles were incomplete and for whom ‘assumed values’ were inserted where a risk factor datum was either missing or out of date. During this time I was influenced by existing CVD risk assessment software designed for use on individuals rather than for populations like e-Nudge. These tended to input one single value for a missing datum, e.g. 1.0 for HDL cholesterol. Slightly more elaborate options would define different values for different genders, but these were still fairly limited. This area interested me for two reasons. Firstly, I was aware from personal communication that Tom Marshall at the University of Birmingham was developing means of basing such assumptions on other existing information in the record. The Sandwell project that he led used this approach and was later published in *BMC Public Health* (10). He would, for instance make an assumption for missing diabetes or smoking status data based on age, sex and other variables that were recorded. Secondly, it was an area that I had discussed with Lucila Ohno-Machado prior to the publication of our own paper (11), which proposed more complex algorithms to account for incomplete primary care data. However, in finalising the e-Nudge software, time was too limited to develop such approaches beyond the imputation of gender-specific assumed values for total cholesterol, HDL cholesterol, and/or systolic blood pressure based on their median levels from the entire 50-75 year age range in the Health Survey for England 2003. This might have been refined to identify such assumed values based on 5-yearly age bands, or on other risk factor values. Smoking status was simply assumed to be ‘Non-smoker’ if absent, and this again might have been improved.

More recently, a key paper has been published by Sterne et al (12) specifically addressing this problem of missing data in the context of cardiovascular disease risk. It followed the first QRISK article (13), whose risk estimates were carried out with only

50% of HDL cholesterol values available (see also Sterne et al: Multiple imputation needs to be used with care and reported in detail, *BMJ Rapid responses*, posted 21.8.07). This is a clearly non-trivial issue. More importantly, the problem of imputed data values was later found to be the source of the implausibly low CVD hazard ratios for total cholesterol/HDL in QRISK, an outcome that immediately questioned the validity of the algorithm (Richard Peto, Doubts about QRISK score: total / HDL cholesterol should be important, *BMJ Rapid responses*, posted 13.7.07). This required a repeat analysis as QRISK2 (14). The Sterne et al paper identified the important issue that participants with missing data do not necessarily represent the same population (in terms of their risk factor distribution and average risk) as those with complete data.

One further point relevant to the ‘missing data’ issue is the problem of estimating risk based on *single values* of risk factor variables such as serum cholesterol. Reynolds and colleagues (15) highlight the wide confidence interval for a risk estimate, so that an estimated risk value of 20% may have a 95% CI of 14%-26%. Basing risk on the average of multiple measurements reduces this confidence interval, but individuals may have only a single cholesterol value available in the record to support the estimate. Such values may be used as a basis for advice on treatment without the clinician necessarily being aware of this variation.

## 9.5 Feedback from students

Since commencing the e-Nudge trial I have discussed its design and implementation on a number of occasions in formal presentation settings. On four of these, all involving Masters teaching programmes at the University of Warwick, I have set the students an exercise. Having described in some detail the design of the trial, I have given them the opportunity in break out groups to discuss the question: *Why might the e-Nudge intervention fail to influence cardiovascular event rates over the timescale of the trial?*

The aggregated responses to this question have been useful in informing my own thinking about how such a trial design might be improved. The responses are varied in their details but can be distilled under the following eight headings:

1. **The clinicians don't respond to the alert messages or the lists, i.e. neither of these change clinical practice.** This might occur due to lack of interest in, or perceived importance of the messages, particularly in the everyday environment of primary care, or to competition between these and other reminders for the clinician's attention. It might also result from skepticism over whether the Framingham algorithm is useful in today's clinical environment, where issues that it does not account for (such as body mass index or waist circumference) arguably receive at least as much discussion.
2. **The reminders might change clinical practice, but not patient behaviour.** Even if an e-Nudge alert triggered a clinician to instigate a risk lowering intervention, lack of responsiveness to the issue by a person who had visited the practice to discuss an unconnected problem (and who might actually have no interest in CVD prevention) would offset any e-Nudge effect.
3. **Software problems (e.g. platform instability) might prevent the effective delivery of the intervention.** The currently available clinical software platform might fail for purely technical reasons. The troubleshooting discussed in Chapter 8 covers this issue although the majority of problems were due to e-Nudge software rather than background platform problems, which was what these students had in mind. The problem discussed in Chapter 8 concerning the Coventry 'Bureau' system and its inaccessibility during the trial's outcome data capture was a platform issue but affected the trial data collection, not the effectiveness of the intervention. This was nevertheless an important and useful issue to raise.

4. **The e-Nudge trial won't continue for long enough for its effect to have a measurable impact on cardiovascular event rates.** This aspect is related to several different timescales:

- The time between receiving a reminder message and the delivery of an effective intervention, which might not occur during the same consultation, e.g. prescription of a lipid lowering agent, delivery of a smoking cessation intervention, or effective reduction of blood pressure.

- The time between the delivery of such an intervention and the benefits this may have on CVD risk. The shortest recorded timescale for a significant impact through lipid lowering is the recently reported JUPITER trial (16) that was halted after a median follow up of 1.9 years. The effectiveness of blood pressure reduction on stroke rates was evident soon after successful reduction in diastolic pressure in the early trials of antihypertensive drugs summarized by Collins et al (17).

- The turnover of registered patients in the practice. If a high proportion of patients were to move from the practice each year to be replaced by newly registered patients then the effectiveness of the e-Nudge on CVD risk would be reduced at the practice population level even though individuals later emigrating from the trial area might still benefit in an undetectable way.

5. **The variables used to determine risk are not the best selection from those available.** It could be the case that in 21<sup>st</sup> century UK practice the Framingham risk factors used in e-Nudge are not an effective means of identifying the highest risk population. Given the efforts recently made to improve this algorithm (described earlier) this is not an unreasonable suggestion. A related issue involves the very concept of *targeted* risk reduction. The case has been made that as most events actually occur in low or intermediate risk groups (because of their greater numbers), CVD prevention

initiatives based on targeting higher risk groups will be less effective than a non-targeted population approach. Marshall and Rouse (18) modeled six different strategies to address the problem of CVD risk reduction in primary care. They concluded that the use of existing data (with assumptions for missing data points) to prioritise individuals for risk assessment could improve efficiency above screening the entire unselected population, particularly in terms of staff time. However, an approach based on intensive treatment of higher risk individuals would be less efficient than one that offered low cost drugs to many people.

6. **The variables used are the most appropriate ones, but are not sufficiently modifiable.** It is possible that a risk algorithm such as e-Nudge could identify the highest risk individuals, but that their risk depends largely on factors that are non-modifiable, such as age and sex. This is indeed a common criticism of the Framingham algorithm used in e-Nudge, although risk can be modified by lipid lowering or anti-hypertensive medication even though this may have little calculable effect on the post-treatment risk score. Indeed, according to some current opinions we should use raised CVD risk as the *only* basis for the decision to use lipid lowering or anti-hypertensive drugs rather than a person's pre-treatment levels of cholesterol and blood pressure (19, 20).

7. **The risk factor measurements taken and recorded in general practice are not a good reflection of the actual variable values.** Risk factor values are recorded (and used as a basis for risk estimation) that are only an approximate (and perhaps less than adequate) measure of the true values. The issue of variability within individuals in serum cholesterol levels over time and its impact on estimated CVD risk has already been discussed above. This variation adds to the effect of laboratory measurement error on a single sample. Both of these effects introduce a random element, reducing the accuracy of risk estimates without necessarily introducing systematic bias. But the



validity of blood pressure measurements has been discussed ever since the MRC trial of mild hypertension reported in 1985 (21), which highlighted the potential for subjective interpretation. The Hawksley random zero sphygmomanometer was used to remove such bias from the measurement of blood pressure in the trial. Following the advent of target based payments for control of risk factors through the Quality and Outcomes Framework, the question of ‘game-playing’ over the recording of blood pressure measurements has been raised (22). In 2009 a UK general practitioner was removed from the medical register for fraudulently inventing data to improve QOF performance (23). To clarify this issue, the blood pressure measurements stored in primary care research databases might be subjected to the same techniques (described in Chapter 2) used by the MONICA investigators to quality check blood pressure data. These included the *last digit preference* and the *proportion of identical duplicate measurements*, both readily accessible electronically recorded data.

**8. The statistical model used to identify high risk individuals is not adequate.**

It is possible that even where the strongest independent risk factors are known and used, and other less independent but still relevant factors are included, the risk algorithm fails to identify the highest risk individuals because the statistical model does not combine them in the most effective way to optimise risk estimation. This issue applied to CVD risk is still a theoretical one, important to identify and discussed in Chapter 2, but generally beyond the overall scope of this thesis.

The students own initial suggestions fell into the first four of these categories, and the final four only came out through further discussion. In the case of the third heading (related to platform instability), I had not personally identified this as a potential barrier prior to these exercises. Whilst aware of potential (and actual) software problems that required correction in the preparatory phase of the trial, I had not actually doubted the

stability of the clinical software system on which the e-Nudge itself ran. But this issue is an important one and platform stability is often taken for granted in primary care.

## **9.6 What would a revised e-Nudge trial design look like?**

The practical issues discussed above made me reflect on how the trial design might have been improved. The systematic review was also important in identifying features of such reminder interventions that may predict successful outcomes. A fresh attempt to test the effect of the same type of intervention whilst addressing these issues would involve the following refinements:

- The sample size would be large enough to make cluster randomisation (with its ‘design effect’ on the sample size) possible, removing any risk of contamination. A much higher number of practices would offset the risk of inadequate risk stratification mentioned earlier. Recruitment over a wider area of the UK would also address any uncertainty over the generalisability of the results to the UK population although the e-Nudge trial population represented a broad demographic mix and its external validity has not been questioned.
- The intervention would be applied exclusively to the primary prevention population, i.e. those with no past history of a CVD event. It would be confined simply to the e-Nudge Groups 3/A and 2/B, i.e. those either with complete data and a raised estimated risk, or those with incomplete data but potentially at high risk based on imputed values for the missing data. This primary prevention focus might help engage the attention of practitioners in a way that a multifaceted intervention might not.
- The CVD risk algorithm would include only CHD and cerebrovascular outcomes as these would correspond exactly with the study outcome measures.
- The imputation algorithm for assumed values of missing data would be refined to maximise the influence (where justifiable) of known correlations between risk factors

in the profile. This could be done in a more detailed way than the e-Nudge algorithm, in the way suggested by Tom Marshall (24) (and personal communication), by imputing values for missing data based upon the patients other, known factors. If possible, it might go beyond this to utilise a more complex algorithmic process to derive such estimates by drawing on known correlations between risk factors that may be inconsistently recorded. But for the purposes of an intervention trial such complex approaches might be unnecessary. The assumption of missing values based on a ‘best guess’ available through simple approaches might be perfectly adequate.

In addition to these adjustments, a new trial might more adequately assess the behavioural influences relevant to the use of screen reminders. Existing literature might inform this approach. Menke et al suggest that from the user perspective screen reminders are ‘carrots, sticks, or flies’ (25). They may encourage a response by offering help, force a response, or be simply ‘swatted away’ with a mouse click. These authors emphasise that successful design of screen alerts requires an understanding of the way that such reminders are likely to affect the user.

A further challenge is the integration of automated reminders into clinical workflow. Kawamoto et al, as mentioned earlier in Chapter 1, identified this factor as among the most important determinants of the success of computerised decision support systems (26), whilst Maviglia et al regard it as the most difficult of all the numerous obstacles to the success of such systems in chronic disease management (27).

Dexheimer and colleagues used a 46 item questionnaire to investigate emergency department clinicians’ attitudes towards screen reminders prior to the implementation of an intervention to promote pneumococcal vaccination (28). This study again highlights the relevance of the health care setting as well as the clinicians’ attitudes as determinants of likely responsiveness. Whilst the emergency department was seen to be an appropriate setting for vaccination, and vaccination was believed to be cost-effective, time constraints and the availability of relevant information determining eligibility were found to be important obstacles.

Mayo-Smith and Agrawal reviewed the literature concerning the factors likely to promote responsiveness to reminders and identified a number of potential characteristics of the reminders, practices, and users (Table 9.1). They then undertook a large study of clinicians exposed to a newly introduced system of reminders in the New England VA Healthcare system (29). They were able to correlate the provider and practice characteristics with the likelihood of completing the suggestions displayed by the computerised reminders. By undertaking a postal survey, they were also able to incorporate provider attitudes into this analysis. Interestingly, no single attitudinal characteristic was found to be important in this study. However, feedback to providers, and the incorporation of support staff into clinic processes were associated with very significantly improved reminder completion rates.

<b>Reminder characteristics</b>
<b>Possible facilitating factors</b>
Minimization of keystrokes, mouse clicks, scrolling, window changes and complexity
Facilitation of alert completion with pre-populated alternatives
Minimization of time required to document why reminder did not apply (“exceptions entry”)
Correct assignment of patient eligibility with updating easy and rapid
Utilization of stored patient data to more precisely target patients
Selective targeting of users based on department, degree and other user characteristics
Provision of enough information to allow a triage decision at a glance
Presence of links to other information resources
Provision for users to have some control of reminders so that they can avoid unnecessary ones
Presentation of CR in use of electronic medical record at the point of decision and action
Including all clinically appropriate options for action, including patient refusal
Ensuring CRs easy to locate in EMR
<b>Practice characteristics</b>
<b>Possible facilitating factors</b>
Easy accessibility to computers
Presentation of CRs at the appropriate time within the clinic workflow to the appropriate staff
Coordination between nurses and providers
Limitation of number of reminders to minimize “reminder fatigue”
Ability for providers to document problems with CRs and receive prompt

feedback
<b>Possible inhibiting factors</b>
Provider workload and inadequate time during visit
Interference with provider-patient interaction
Use of paper records or forms in completion process
Using reminder while not with patient
Slow computer processing time
CRs that benefit administration more than providers
Lack of reimbursement for reminder completion
<b>User characteristics</b>
<b>Possible facilitating factors</b>
Adequate training on reminder use
Staff provider vs. resident physicians

*Table 9.1 List of factors identified by Mayo-Smith and Agrawal (29) in the published literature potentially determining effectiveness of computerised reminders (CRs).*

Taking these issues into account, pilot work that assessed clinician responsiveness and the successful integration of the proposed intervention into the workflow might usefully inform the design of the final product if a future trial of reminders supporting CVD risk reduction were to be planned on a larger scale in the UK.

Health economic implications are also important, and were not assessed in the e-Nudge trial given the time constraints. Differences in prescribing and referral patterns between the trial arms might have detected influences of the intervention on clinical behaviour in ways that were not visible in the trial.

The issue of potential harm was also not assessed, other than through the field notes recorded during discussions with practice teams, including the one practice that withdrew. As well as interference with the visibility of other information on the screen discussed in Chapter 8, the potential for screen reminders to lengthen consultations is a quantitative outcome that could be measured fairly easily in this type of trial.

Qualitative methods would be required to determine whether such added consultation time was, or was not welcomed by clinicians and patients. In particular, the question over whether the latter group considered this a threat to personal autonomy, as suggested by Getz (30) and discussed in Chapter 3, would be an interesting and important matter to investigate.

## 9.7 Summary

The e-Nudge trial and associated research identified a number of issues determining the ability of a software intervention installed in general practice systems to facilitate CVD risk reduction during routine primary care. The trial demonstrated a significant effect in improving data adequacy through influencing practice team behaviour, but did not demonstrate within two years an effect on CVD event rates. To do so would probably require a larger sample size, a longer timescale, and a more focussed intervention confined to the primary prevention population. Through the conduct of this research various other issues came to light. These concerned the importance of the data source, the processes of care on which a pragmatic trial of this type depends, their vulnerability to health policy changes during a trial, and the relevance of perspectives originating from unexpected sources.

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## Chapter 10: Outputs of the research

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### 10.1 EMIS software for recognising undiagnosed diabetes

A major output of this research was the design of a software module to assist in the early detection of diabetes using electronic data in primary care. This module resulted from the QRESEARCH project described in Chapter 8, triggered by the e-Nudge trial's preparatory phase, and was subsequently installed in all 5000+ EMIS practices across the UK (1). In a subsequent paper in the *British Journal of Diabetes and Vascular Disease* I described how these two projects had led to this outcome, and provided the projected numbers of people in the overall UK population at risk of undiagnosed diabetes identifiable through this approach (2). This number (528,000) is comparable with the estimated figure for the undiagnosed diabetes population (up to 1% of the total UK population based on one source (3)). The installation of this module in practices as a standard component of EMIS clinical software allows such individuals to be recognised during routine care, either opportunistically through screen messages or more systematically using regularly updated lists, very much in keeping with the e-Nudge approach. The QRESEARCH searches required for this project were carried out during June 2006. Whilst it would take until March 2008 to publish the paper, the EMIS software was installed in all of their sites and linked to screen alerts by April 2007. This development was the first example of a new algorithm based on nationwide primary care data resulting in a system of screen reminders to assist in identifying risk of disease.

Whilst another software provider (Vision) has independently developed a similar module to support case finding for diabetes under the QOF, only EMIS have nationwide data (due to these projects) on the numbers of people identified and (perhaps more interestingly) the time interval since the measurement of the abnormal

blood glucose level in affected individuals. The Vision software needs to be actively configured to provide screen alerts, whilst the EMIS reminders are a non-optional feature of their software considered essential for clinical safety (David Stables and Shaun O’Hanlon, personal communications).

In 2008 I applied to Diabetes UK for a project grant to test the effectiveness of the EMIS software at detecting confirmable cases of undiagnosed diabetes. This project was designed to identify a sample of patients in a demographically diverse selection of EMIS practices and test them for diabetes using fasting glucose measurements or oral glucose tolerance tests where appropriate. The objectives were to measure and report the ‘number needed to screen’ to detect one new case of undiagnosed diabetes in this subgroup of the practice population – those not on the diabetes register but whose most recent blood glucose level was either frankly raised (in the diagnostic range for diabetes) or borderline and justifying follow up testing. Such patients are now readily identifiable in the computer system of any EMIS practice, through the lists created and maintained by the new software. My aim was to replicate the approach of the New Zealand study investigators (4) who had randomly targeted householders in an ethnically diverse region of South Auckland and tested them for diabetes after initially measuring random blood glucose levels. These researchers had demonstrated that random blood glucose measurements were superior to traditional risk factor profiles as a means of identifying those most likely to benefit from screening for diabetes (e.g. by oral glucose tolerance test), particularly in the European population.

However, the Diabetes UK application was unsuccessful. One problem in the design was the issue over whether a research funder should be responsible for paying for the necessary blood tests when their clinical justification was clearly evident and expected under current guidelines. Another problem was over whether a general practitioner inviting a patient to take part in the project (through having his/her diabetes status clarified) should potentially confuse the clinical need for this clarification with the usual patient’s right to consent (or decline) to take part in a research study. Testing

patients identified by the software for diabetes was clearly justified on clinical grounds and not required merely to answer a research question. The Warwickshire Research Ethics Committee approved the application but deliberated over whether the project was in fact audit or research, as it was designed to collate information (blood glucose results) from multiple practices that involved data collected (albeit systematically and prospectively) in a clinical rather than a research setting.

A potentially important research question therefore remains unanswered. I suspect that the 'A' and 'B' lists in the EMIS software are likely to provide the highest yield of undiagnosed diabetes cases of all the electronically identifiable subgroups of a practice population in UK primary care. However, this impression is unproven and needs to be reworked into a new research proposal. Since 2008 when the original application was declined, a new algorithm (the QDScore) for identifying patients at risk of future diabetes has been published (5). This is similar in its risk factor profile to a previously published algorithm designed for targeted case finding (6). Whilst there is an important distinction to be drawn between prevalent undiagnosed diabetes and future incident diabetes, it would be interesting to compare these algorithms with the EMIS 'A' and 'B' lists in their ability to identify undiagnosed cases.

## **10.2 Advice to the National Institute for Health and Clinical Excellence on CVD risk estimation in primary care**

In 2006 I was approached formally by the Guidelines Development Group for the National Institute for Health and Clinical Excellence (NICE), who were considering evidence provided by an academic advisor on CVD estimation using primary care data and required peer review. This invitation gave me the opportunity to allow my experience of e-Nudge to influence what became an important policy document, the 2008 Clinical Guideline 67: Lipid Modification (7).

### **10.3 e-Nudge as a software option in UK general practice**

On a less formal basis, I was able to feed into UK policy on the emerging vascular screening programme through contacts with the authors of *The Handbook for Vascular Risk Assessment* (8). This manual described a small number of software options available in the UK for identifying individuals at raised cardiovascular risk, and includes a description of the e-Nudge. Of all these options, e-Nudge is the only one that has been subjected to a randomised controlled trial.

### **10.4 The EMIS Primary CVD Prevention toolkit**

Following the e-Nudge trial, I prepared and submitted to EMIS a brief advisory document describing means of meeting the needs of the National Vascular Screening Programme and more specifically NICE CG67 (Lipid Modification) within primary care, based on the e-Nudge experience. This experience has fed into the development of a new EMIS module, the Primary CVD Prevention Toolkit, which builds lists of patients at risk based on existing data, and also those in need of further data collection, very much in the style of e-Nudge. The risk algorithm used is QRISK2 rather than Framingham. My advice had been that both QRISK2 and Framingham might be optionally available to practices, as the current guideline (NICE CG67) still recommends Framingham as the tool to support case finding under the vascular screening programme.

### **10.5 GE Healthcare searches**

As a result of the international publicity surrounding the QRESEARCH project published in 2008, I was approached by GE Healthcare (a subsidiary of General Electric) to explore the use of the same approach in their US 'Centricity' database. This database hosts just over 11 million electronic medical records from a variety of source health care organisations (including over 9,000 ambulatory practices) across the US.

The Medical Quality Improvement Consortium (MQIC) has access to run queries on the Centricity system for research as well as clinical purposes.

Initial searches (using the same 'A' and 'B' protocols as the QRESEARCH project) were carried out by GE Healthcare. These suggested that large numbers of individuals with possible undiagnosed type 2 diabetes are also identifiable in the US. The GE team presented these findings (in a direct comparison with our QRESEARCH project) at the Conference of the International Society of Pharmaco-economics and Outcomes Research, Paris, in September 2009.

This US based result suggests that individuals with biochemical evidence of undiagnosed diabetes may be identifiable in other health settings outside the UK. This is not simply a result of the failure of health care providers. It may be due to the fact that borderline blood glucose levels, whilst a serious health concern, are commonplace, generally asymptomatic (or producing very low grade symptoms), and may be missed in people who are either 'hard to reach' or are, as well as their health care providers, focussed on more obvious immediate demands.

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## **10.6 Publications and dissemination**

Seven peer-reviewed publications resulted from this PhD research (1, 2, 11-15), including the final report that was in press when the thesis was submitted. I also plan to publish the systematic literature review described in Chapter 4. As well as publishing in journals, I have disseminated this research through the following channels:

- 1. Formal academic presentations.** These included regional events including the South West SAPC conference (18.6.09), in which I presented the results of the e-Nudge trial. On earlier occasions the design of the trial was presented at SchARR, University of Sheffield (3.6.06); McGill University, Montreal (6.11.06); Moncton University, New Brunswick (10.11.06); and the Coventry and Warwickshire Cardiac Network 'Good

Practice Day' at the Ricoh Arena (16.5.08). The Canadian visit was funded by the University of Warwick's North American Collaboration scheme.

2. **Feedback to the Primary Care Trusts.** Formal feedback to PCT Executives over updates on the e-Nudge trial was presented at three meetings designed to strengthen collaborative links between the University of Warwick and the local NHS.

3. **Feedback to practices.** At each stage the participating practices have been kept aware of the outcomes and impacts of the trial. PDFs of published articles have been forwarded to them on each occasion.

4. **Feedback to policy makers.** As discussed above, I was invited to contribute towards the development of the NICE CG67 Guideline and with the group that produced the Handbook for Vascular Risk Assessment.

5. **Media publicity.** The recognition of undiagnosed diabetes in the QRESEARCH study was disseminated in the lay press throughout the UK as well as internationally (e.g. news websites in Germany, Australia, Sri Lanka).

6. **University of Warwick i-Cast.** The University arranged for an i-Cast to be filmed to illustrate the story of how the initial e-Nudge work resulted in a nationally distributed software module. This featured a patient of mine who was identified by some preliminary searches in my own practice as having undiagnosed diabetes. He went on to lose several stones in weight, effectively reversing his hyperglycaemia. The i-Cast is available at:

[http://www2.warwick.ac.uk/newsandevents/pressreleases/gp146s\\_databases\\_could](http://www2.warwick.ac.uk/newsandevents/pressreleases/gp146s_databases_could)

## 10.7 Summary

This chapter has described some outputs of the e-Nudge research including national impacts. The final chapter will summarise the main conclusions of this research and outline potential future directions.

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## Chapter 11: Thesis summary and future research directions

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### 11.1 Overall conclusions of the research

The original aim of this research was to investigate the potential of routinely collected general practice data to support a programme of cardiovascular risk reduction in the UK. Major questions concerned not only the completeness of existing data (completeness in the sense of fulfilling the minimum requirements of a basic Framingham calculation) but also its quality, its accessibility to primary health care professionals, and its utility as an input to software programs designed to compute risk. Other issues included ethical aspects related to the process of risk assessment and its potentially negative consequences. Finally, I questioned whether electronic reminders and flagging mechanisms in the primary care environment could influence clinical care in a way likely to reduce future cardiovascular events. This question was developed into a randomised controlled trial that became the main focus of the research, together with a systematic review of similar interventions applied to health care contexts.

#### 11.1.1 Two stage process of risk estimation

Preparatory work discussed in Chapter 5 was extremely useful in guiding the design of the e-Nudge trial as it helped to identify problematic areas such as the definition of an ex-smoker. It was through this pilot work that I became aware of the distinction between the process of *prioritising* candidates for risk assessment and the process of *clarifying and confirming* their risk level through more detailed assessment. This PhD project has confirmed that routinely collected data are extremely useful for the first stage but less than adequate for the second. In a rapid response to the initial QRISK paper, McManus and Mant drew a similar distinction, and suggested that different algorithms may be appropriate in different settings, QRISK for identifying high risk

groups at the population level, and Framingham for estimating the risk of an individual patient [McManus R and Mant J, Setting for risk calculation will affect performance of QRISK. *BMJ Rapid Responses*, posted 21.8.07].

### **11.1.2 Adequacy of data**

The e-Nudge trial itself informed two issues that were important for current practice. The first of these concerned the baseline data following software installation, which provided a comparison between the proportion of the over 50 year old population having ‘complete’ profiles (as defined above) with those whose profiles would require more data for a basic risk estimate. These results suggested that whilst a readily identifiable population exists whose raised risk is already evident through existing data, the group is outnumbered perhaps 4 or 5 times by those possibly at raised risk but requiring further data to estimate risk. It also suggested that the group whose raised risk is already evident (a group that includes those whose major risk factors are their age and sex) is significantly smaller than those with existing cardiovascular disease and *modifiable* risk factors that are out of target (1).

### **11.1.3 Impact of electronic reminders**

A systematic review of literature on controlled trials of reminder interventions aiming to influence the behaviour of clinicians in the consultation environment found their impact to be generally positive. The effect was variable, usually modest and appeared to be dependent on the health care context. Specific factors consistently predicting the effect size were difficult to identify.

Electronic reminders incorporating a cardiovascular risk algorithm and drawing on routinely collected UK primary care data were tested through the e-Nudge trial. This demonstrated that such reminders can improve the adequacy of risk factor information during everyday care to improve the visibility of the at risk population for risk reduction. At the same time, the group requiring further data to calculate risk was

reduced. However, hard clinical outcomes such as the cardiovascular events that were the primary outcome measure were not significantly reduced.

#### **11.1.4 Lay perspectives**

Whilst the e-Nudge trial was running, I began investigating some of the qualitative issues including the attitudes of lay people towards risk assessment. This work is included only to provide context for the main research question and as a pointer to future research directions. The interview transcripts reported in the Appendix provided evidence of a range of opinion over the value of primary cardiovascular risk reduction. Whilst the overall feeling was very positive, some of the participants were less enthusiastic when the practical implications were discussed. This study was very limited and served only to provide me with some insights into the value of including qualitative work as part of a clinical trial.

#### **11.1.5 Contextual basis for CVD risk estimation**

A further insight gained through this research relates to the shift in UK health policy towards a broader understanding and concept of cardiovascular risk. This process began with the focus in the 1970s on a small number of independent CVD risk factors, and in particular on the probably causative, and certainly modifiable factors. The need to develop effective preventive interventions (including drug therapy and lifestyle change) required the identification of causative factors, as it would only be by modifying these that CVD risk could be reduced. But interestingly, the emphasis has since shifted towards the identification of risk on the basis of all relevant factors, including those associated with but not necessarily causally linked with CVD outcomes. Overlapping (i.e. non-independent) risk factors are now considered important markers in modern algorithms, such as ethnicity, family history, and social deprivation. This approach has resulted from the finding that preventive interventions tend to produce a fairly consistent *proportional* reduction in absolute risk. If everybody's absolute risk is

reduced by a quarter by an intervention, those most likely to benefit are those with greatest initial absolute risk, even when this risk is estimated using non-modifiable factors. This contextual approach supports a more complex basis for defining risk, and the use of algorithms that utilise factors that are at least partially redundant (in a statistical sense) to define the at risk population. This conclusion is fundamental to recent changes in health policy in this clinical area.

### **11.1.6 Responsibility to act on identifiable at risk groups**

In Chapter 3 I discussed the responsibility felt by care givers and the priority given by policy makers created simply by the *ability to identify* at risk individuals, particularly in life threatening scenarios. The ‘Rule of Rescue’ holds (rightly or wrongly) that identifiable individuals should take priority over those whose needs may be equal but who are not identifiable, or at least not currently identified. This approach is not generally considered valid by ethicists, but nevertheless influences policy makers and clinicians on a more intuitive level. This issue arose in a number of ways during the process of the e-Nudge trial.

First of all, the Ethics Committee required reassurance that it was ethical to withhold the potential benefits of identifying raised CVD risk in the control arm. Control patients were being identified as frequently as intervention patients (at least initially), and yet no flagging mechanisms would be triggered. The committee were reassured that the trial’s control arm would continue to benefit from ‘usual care’ i.e. that the practice teams could continue to assess and address CVD risk in these people as they had done in the past. They had access to the same range of risk factor data. I was simply trialling the additional effect of the e-Nudge software. But an interesting dilemma had been created by applying an algorithmic process to the data, a dilemma that had not apparently arisen beforehand, even though all of the data existed. The patterns were already present in the data but couldn’t easily be perceived by human clinicians (2). Did this relinquish the responsibility of clinicians to respond to them?

One might take the view that the e-Nudge is, as discussed below, a pattern recognition tool of significantly greater complexity than the majority of search protocols in common use (as it requires a weighted computation of data inputs), but it is likely that in the foreseeable future such approaches will become commonplace.

This raises the question over whether the *complexity* of the search algorithm determines any resulting responsibility. The identification of patients at risk of CVD using the Framingham algorithm was a sufficiently complex approach algorithmically that it represented a significant departure from ‘usual care’, and as its utility had not been proven, it justified trialling. However, when the baseline data demonstrated that a significant group with possible undiagnosed diabetes was identifiable through a relatively simple search technique (comparable in complexity with many of the everyday searches undertaken in general practice), it was not considered ethical (by myself nor by EMIS) to identify such individuals in the control arm without taking action. The QRESEARCH project that followed this finding used an even simpler search protocol (3), detecting a still more significant number of individuals. In the press coverage that followed this finding, I emphasised the *simplicity* of the search technique that we had shown could uncover such widespread unmet health need. It was this simplicity that made the discovery newsworthy, and that then entailed a responsibility for practice teams to correct this apparent shortfall in care. As time goes by, more complex algorithms are becoming available to identify similar at risk groups, including the recently published ‘QDScore’ for future diabetes risk (4). This algorithm identifies those at risk of *future incident* diabetes rather than *prevalent undiagnosed* diabetes, and does not therefore hold the same ethical requirement for early action (although it could be argued that the risk factor distributions of these categories overlap strongly). However, it seems likely that in future, health care providers taking responsibility for large electronic databases may feel responsible also for acting on the algorithmically accessible patterns within them.

In May 2009 I was invited to attend an EPSRC/MRC funded workshop entitled ‘Grand Challenges in Information Driven Health: An innovative multidisciplinary patient-centric early detection care model’ organised by Cardiff School of Computer Science and Cardiff School of Medicine. Its aim was “to define a research agenda capable of delivering the technology, informatics and service model necessary to provide the best community-based care for patients with chronic conditions in the future.” Without anticipating the published report (still in preparation) from this event, one issue arose that concerned our general responsibility for recognising patterns in health data, data that might be largely owned and kept by the patient, given the development of patient held records. A concern was shared that responsibility for acting on such patterns might in future exist whether or not we had actually utilised the necessary programme to identify them. At an early meeting with a practice that I recruited for the e-Nudge trial, one general practitioner raised the related question of his clinical duty to respond to the intervention patient alert messages, simply because the patients (already *potentially identifiable* using existing data) had become *actually identified*. It occurred to me that in a situation of increasingly adequate data, three categories of pattern might exist: unidentifiable using currently conceived or available algorithms; potentially identifiable (algorithm available but not actually executed); and actually identified. Our responsibility to these groups is perhaps no longer confined, as it may have been in the past, to the final one.

## **11.2 Potential for development of the e-Nudge approach to other clinical areas**

### **11.2.1 Algorithmic identification of at risk groups**

The e-Nudge algorithm included the Framingham cardiovascular risk equation. Risk factors were automatically extracted from electronic records and fed into this equation

to yield a risk estimate as the output. This model of pattern recognition is more complex than most other forms in current use. For the majority of such tasks in primary care, searches are run to identify certain groups, subgroups of these groups, and perhaps subgroups of these subgroups. For example: patients with diabetes; the subgroup with a recent blood pressure measurement; then the subgroup with a recent blood pressure measurement that is out of a defined target range. In other cases a number of different (sometimes overlapping) groups or subgroups are identified. For example, those with diabetes and *either* a blood pressure *or* a serum cholesterol that is out of target. Such approaches require the construction of search protocols involving simple Boolean AND/OR/NOT functions and the SHARED/EXCLUDE/INCLUDE rules built in to general practice computer systems. These are also familiar to anyone used to searching medical literature databases and other electronic resources. But to identify people at risk of cardiovascular disease, the relevant data must not only be extracted but also then fed into an algorithm typically involving a number of internal parameters including regression co-efficients. During the development of the algorithm these parameters are tuned to optimise the statistical fit between predicted and observed outcomes. Once optimised, variation in the internal parameters is likely to reduce this fit unless a change in the relationships between inputs and outcomes develops over time. This might occur due to a change in population demographics, the clinical pattern of a disease, or the interactions between risk predictors.

### **11.2.2 Identifying risk of other conditions**

Cardiovascular disease prediction has, for reasons discussed in earlier chapters, lent itself well to this more complex approach, but various other areas also show such potential as the quality of primary care data improves. An example is the MDRD (Modification of Diet in Renal Disease) algorithm for calculating estimated glomerular filtration rate (e-GFR) (5). This was introduced as a software tool into practice systems due to the requirement of the quality and outcomes framework for practices to identify



those with chronic kidney disease (CKD) grades 3-5. Rather like the e-Nudge search lists (available to practice teams for intervention patients) the MDRD lists are available in EMIS and other systems to assist practitioners in creating CKD registers. But despite the fact that general practice data are useful for this purpose (6), this tool is unable to adequately define the CKD population without individualised adjustment of risk assessment. It is able to identify likely cases on the basis of age, sex and serum creatinine (all factors that are well supported by electronic data in primary care), but to be confident of the e-GFR value other factors should be included that are less well supported. These include black African ethnicity, which is still not reliably recorded in general practice for many people. Extremes of muscle mass are also relevant and not accounted for in the algorithm, which makes a generalisation about the relationship between muscle mass and age.

Laboratory software used to estimate e-GFR does not necessarily contain information on the patient's sex, unlike the database of the general practice requesting the test, but only their name on the request form. In reporting e-GFR, it may therefore advise on adjustment of the MDRD estimate if the assumption it has made about the gender of the patient is incorrect. This is a further example in which an algorithmic computation is made on the basis of incomplete or uncertain data, where the missing 'value' (in this case gender) is not known with sufficient confidence to produce a definite estimate, and may require clarification by a practitioner receiving the report. In addition, a clinician might consider whether the serum creatinine measurements on which the e-GFR values have been derived were typical for the patient and likely to remain so. It is recommended that two abnormal values should be used, spaced at least three months apart as a basis for inclusion on the CKD register. However, the particular circumstances of the individual patient may determine whether such inclusion is appropriate, circumstances that are only evident through examination of the patient record by a human clinician. CKD registers cannot be automatically created solely by

practice based software, and the same issue applies to 'At risk of CVD' registers. This is an important conclusion of this thesis.

Looking to the future, risk of malignancy, osteoporosis, hospital admission, and mental health problems are all possibilities for the automated (but provisional) creation of 'at risk' registers, based on electronic data but probably requiring human interpretation. In these examples the relevant risk factors are either less well known or less well recorded than those for CVD risk. However the increasingly adequate recording of outcome data in general practice (and other primary care sources such as Primary Care Trust) databases may provide a basis for the future targeting of at risk individuals in this setting.

### **11.3 Towards a nationwide adaptive prediction tool for cardiovascular disease prevention**

My original paper co-authored with Lucila Ohno-Machado (7) discussed the future possibility of a nationwide adaptive prediction tool for cardiovascular disease prevention. This model became a personal benchmark for the progress of my research to date. Through such a tool changes in the relationships between risk predictors, their interactions, and the relevant outcomes would be detected automatically and fed back to primary care practitioners to tailor risk reduction strategies adaptively in response to evolving population demography and risk patterns. Other advantages that we identified included a wider potential range of risk factors than the traditional ones, and the use of more complex algorithms capable of detecting interactions and imputing missing data more effectively. The e-Nudge project attempted to investigate and establish a major element of this approach, the application of a risk algorithm to 'live' primary care data linked to screen alert messages to assist in the recognition of at risk individuals and to improve risk factor data quality during routine care through feedback to practitioners.

A further element of this model was that locally collected information on such risk factors could be fed into a nationwide data collection system to develop a UK based cardiovascular risk algorithm tailored to local patterns. This element was later achieved by the QRISK team led by Julia Hippisley-Cox (8, 9). QRISK2 includes major risk factors not included in the Framingham equation such as body mass index, social deprivation, ethnicity, family history of cardiovascular disease, atrial fibrillation and rheumatoid arthritis. The QRISK project enabled routinely collected UK data to assist in the tailoring of cardiovascular risk predictions to the UK population.

One result of both the e-Nudge and the QRISK projects was the development of a 'Primary CVD Prevention Toolkit' installed in all EMIS systems across the UK in March 2009 and described in Chapter 10. This provides for the identification of at risk individuals (according to QRISK2) in practice databases. The QRISK2 algorithm has the potential to be adjusted over time if changes in risk factor patterns are detected through the QRESEARCH database. It is not yet linked to screen alert messages (as cardiovascular risk assessment is currently only required for the QOF for newly diagnosed patients with hypertension), but most of the elements anticipated by the original paper (7) have now occurred. The next question is: what further work is necessary to fulfil the vision of a nationwide adaptive prediction tool for cardiovascular disease prevention, and how can this be achieved?

First of all, the EMIS Primary CVD Prevention Toolkit would need to influence clinical care. This might require linkage to screen reminder messages, and is a practical issue. To overcome it, incentives would probably be required to balance the negative aspects of screen messages. Such incentives would translate either to clear, unequivocal clinical need (such as that identified by the undiagnosed diabetes alerts), or financial incentives through incorporation into the QOF. The ethical issues discussed in Chapter 3 would be relevant to policy development in this area. Switching on CVD prevention toolkit alerts would immediately create a significant volume of screen messages that

would need to be managed alongside all the other demands of everyday practice and would not be universally welcomed by practitioners and patients.

The QRESEARCH database can not directly feed its findings back to practices. Information flow occurs in one direction only, as this is a research facility and practice and patient anonymity are essential for ethical reasons. If changes in the pattern of CVD risk were to occur over time in the UK population (requiring adjustments to the QRISK internal parameters) then this would require a further QRISK study to derive and validate an improved algorithm. This algorithm would then need to be installed in practices through a patch transfer from EMIS or other software provider. This could in principle be done quite frequently, although it is a time and resource consuming process. However, my (and Lucila Ohno-Machado's) original idea was that data processing would be a *distributed* phenomenon rather than one occurring in a central repository. It would be a continuous, automated process rather than one depending on a series of retrospective analyses as in QRISK and QRISK2. *Parallel processing* is the underlying paradigm of neural networks (as discussed in Chapter 2) and is the assumed basis for human cognitive function. Local adaptive processing of cardiovascular risk factor data in multiple practices (whilst guided by an algorithm common to all of them) was the basis for the e-Nudge intervention. A further (relatively small) step would be to allow the automated tailoring of the algorithm itself to local patterns in the data.

A future 'adaptive prediction tool' would provide this feedback through ongoing 'learning' of the risk algorithm over time. This process would be continuous rather than intermittent. Changes in the internal parameters of the algorithm would occur without the need for in-depth analysis of past cohort outcomes by human investigators. This thesis suggests that such 'learning' (i.e. the adaptive tuning of algorithm parameters) could only inform 'best guess' identification of the 'at risk' population (due to data quality and other issues). However at the practice level this might still improve targeting compared with an approach based on national cohort study findings applied to current data. This would allow the tailoring of risk prediction to

regional or local populations. Statistical power requirements would limit the population size for such adaptation, but the volume of data present even at the primary care trust (PCT) level, and certainly at the strategic health authority level is far greater than that in the Framingham heart study. The potential need for such regional tailoring within the UK is suggested by the recent derivation of ASSIGN, an algorithm derived from a purely Scottish population cohort (10) and recommended by the Scottish Intercollegiate Guidelines Network for Scotland (11).

Moving on to how such a system might be realised in practice, obstacles include the *unidirectional* flow of information from practices to research databases, and the need for retrospectively identified historical cohort populations on which to carry out prospective observational outcome studies. *EMIS-Web* is a recently developed web-based platform supporting UK electronic health records in an increasing proportion of EMIS practices. Practices connected to EMIS-Web are provided with on-line back up of data transferred in real time to two secure servers hosted by EMIS in Leeds. Unlike QRESEARCH, this information is held for clinical rather than research reasons and therefore includes all patient identifiers. For this reason, feedback of algorithmically determined patterns using all available data (in the form of lists of at risk patients) to practices would be permissible as it would not require the analysis of data by a human researcher. The information would be contained within the NHS and regulated by the governance framework of clinical care. The originally proposed use of the Newchurch system to provide feed back to e-Nudge trial practices remotely (described in Chapter 5), whilst not in the end needed for the trial, was in a sense a ‘test case’ of this principle and was approved by the Local Research Ethics Committee. Demonstrating the effectiveness of such a system at reducing cardiovascular risk (or risk of other conditions) would require a randomised controlled trial on a nationwide level following the development of the adaptive risk algorithm, combining distributed pattern recognition with feed back mechanisms (including screen reminder messages) delivered at the point of care. It would require a programme of research involving clinicians,

practice administrators, computer scientists, information technology technicians, and industrial partners. This is a potential future direction for the research described in this thesis.

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## Appendices

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- A. Results of the Sheffield survey 1997 (referred to in Chapter 5)**
- B. SQL program for the Framingham CVD equation**
- C. Invitation letter to practices for the e-Nudge trial**
- D. Practice letter of agreement form**
- E. The e-Nudge User's guide**
- F. Eight weekly email message sent to practices throughout the trial**
- G. Standard Operating Procedure for data collection**
- H. Data extraction form for systematic review**
- I. Risk of bias table for systematic review**
- J. Patient invitation letter for interview project**
- K. Patient information leaflet for interview project**
- L. Patient consent form for in-depth interview**
- M. In-depth interviews with members of the public**
- N. Articles published prior to PhD registration**
  - a) Holt T, Ohno-Machado L. A nationwide adaptive prediction tool for coronary heart disease prevention. *Br J Gen Pract* 2003;53(496):866-70.
  - b) Brindle P, Holt T. Cardiovascular risk assessment--time to look beyond cohort studies. *Int J Epidemiol* 2004;33(3):614-5.
- O. Articles published during the PhD project (1-6)**
  - 1. Allwood I, Holt T. The South Warwickshire NHS Care Records Service Demonstrator Project: lessons for the National Programme for IT. *Inform Prim Care* 2005;13(4):257-62.
  - 2. Holt T, Thorogood M, Griffiths F, Munday S. Protocol for the 'e-Nudge trial': a randomised controlled trial of electronic feedback to reduce the

cardiovascular risk of individuals in general practice [ISRCTN64828380].

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3. Holt T, Thorogood M, Griffiths F, Munday S, Stables D. Identifying individuals for primary cardiovascular disease prevention in UK general practice: priorities and resource implications. *Br J Gen Pract* 2008;58(552):495-8.
4. Holt T, Stables D, Hippisley-Cox J, O'Hanlon S, Majeed A. Identifying undiagnosed diabetes: cross-sectional survey of 3.6 million patients' electronic records. *Br J Gen Pract* 2008;58(548):192-6.
5. Holt TA. Detection of undiagnosed diabetes using UK general practice data. *Br J Diab Vasc Dis* 2008;8:291-4.
6. Holt T, Holt C. Raised blood glucose concentration. *BMJ* 2008;337:a1073.

# The Sheffield table survey 1997

(adapted from Ohno-Machado and Holt 2004\*)

The Sheffield tables were published in 1996, and consist of rows and columns of cells, each cell representing a combination of risk factor values (age, smoking status, diabetes status, hypertension status, and LVH status). Separate tables are given for men and women. Each cell contains a cholesterol value at which the combination of risk factors would produce a risk of developing coronary heart disease (CHD) of  $\geq 30\%$  in the next 10 years. The cholesterol values were obtained using the Framingham algorithm for calculating CHD risk.

These tables provided a framework for searching a practice population to identify the most appropriate candidates for cholesterol measurement. In 1997 a series of searches (named Sheffield 1-13) were carried out for this purpose on a North Yorkshire population (registered with the Danby Practice). All cells in the Sheffield tables that contained any cholesterol value were used to define the search protocols. Because LVH status was frequently unknown or unrecorded, this risk factor was not included in this survey.

Search	Sex	Hypertension	Smoking	Diabetes	Age (years)	No. identified
Sheffield 1	Male	Y	Y	Y	30-70	0
Sheffield 2	Male	Y	Y	N	34-70	12
Sheffield 3	Male	Y	N	Y	36-70	3
Sheffield 4	Male	Y	N	N	40-70	42
Sheffield 5	Male	N	Y	Y	48-70	1
Sheffield 6	Male	N	Y	N	54-70	29
Sheffield 7	Male	N	N	Y	58-70	3
Sheffield 8	Male	N	N	N	64-70	47
Sheffield 9	Female	Y	Y	Y	36-70	1
Sheffield 10	Female	Y	N	Y	40-70	3
Sheffield 11	Female	Y	Y	N	42-70	6
Sheffield 12	Female	Y	N	N	50-70	41
Sheffield 13	Female	N	Y	Y	52-70	1

Y = Yes, risk factor present  
N = No, risk factor absent

As a result, a total of 189 patients were identified out of a population of 2137 (8.8%) requiring cholesterol measurement. In some cases the cholesterol value would already be known, and this survey's results reflect the distribution of the risk factors in the practice population and not the adequacy of the data. The individuals' notes were then tagged electronically and each patient subsequently invited in for a blood test. Where it would then make a difference to treatment decisions, an ECG was arranged to determine LVH status. The tables made it possible to determine in each individual case whether or not the ECG result would actually affect treatment decisions over lipid lowering therapy.

\* Ohno-Machado L, Holt T. Complex pattern recognition in health data. Chapter in: *Complexity for Clinicians*. Holt T (Ed.) Abingdon: Radcliffe Publishing, 2004.

# SQL program for the Framingham CVD equation

```
drop function Calculate_CVD_10Year_Risk
GO
```

```
create function Calculate_CVD_10Year_Risk (@Age tinyint, @Sex bit, @SystolicBP float,
@DiastolicBP float, @TotalCholesterol float, @HDLCholesterol float, @Smoker bit,
@Diabetes bit, @LVH bit)
```

```
returns float
```

```
as
```

```
begin
```

```
    declare @aa float, @ab float, @ac float, @ad float, @ae float, @af float, @ag float,
@ah float, @ai float, @aj float, @ak float, @al float, @am float, @an float, @ao float, @da
float, @db float, @dc float, @dd float, @de float, @df float, @dg float, @dh float, @di float,
@dj float, @dk float, @dl float, @dm float, @dn float, @dp float,
```

```
        @lnAge float, @lnDiastolicBP float, @lnSystolicBP float, @ChlRatio float,
@lnChlRatio float, @lnTime float,
```

```
        @u float, @mu float, @ro float, @risk float
```

```
    -- Rules
```

```
    --
```

```
    -- Sex (0) is Male, Sex(1) is Female
```

```
    -- Smoker (0) is a Non-Smoker, Smoker (1) is a Smoker
```

```
    -- Diabetes (0) is No Diabetes, Diabetes (1) is a Diabetic
```

```
    -- LVH (0) is No LVH, LVH (1) is LVH
```

```
    -- Basic validation
```

```
    -- Blood Pressure
```

```
    if @SystolicBP < @DiastolicBP
```

```
        -- Systolic lower than Diastolic
```

```
        return (null)
```

```
    -- Cholesterol
```

```
    if @HDLCholesterol > @TotalCholesterol
```

```
        -- HDL more than Total Cholesterol
```

```
        return (null)
```

```
    -- Validation complete
```

```
    -- Set constants for CVD
```

```
    set @aa = 0.6536
```

```
    set @ab=-0.2402
```

```
    set @ac=18.8144
```

```
    set @ad=-1.2146
```

```
    set @ae=-1.8443
```

```
    set @af=0
```

```
    set @ag=0.3668
```

```
    set @ah=0
```

```
    set @ai=-1.4032
```

```
    set @aj=-0.3899
```

```
    set @ak=-0.5390
```

## The e-Nudge Trial Standard Operation Procedure

```
set @al=-0.3036
set @am=-0.1697
set @an=-0.3362
set @ao=0
set @da=0.6761
set @db=-0.2421
set @dc=17.5392
set @dd=-0.8019
set @de=-2.1231
set @df=0
set @dg=0.2584
set @dh=0
set @di=-1.0117
set @dj=-0.3900
set @dk=-0.5365
set @dl=-0.3575
set @dm=-0.1661
set @dn=-0.3847
set @dp=0

-- Initial calculations
set @ChlRatio = @TotalCholesterol/@HDLCholesterol

set @lnAge = log(@Age)
set @lnDiastolicBP = log(@DiastolicBP)
set @lnSystolicBP = log(@SystolicBP)
set @lnChlRatio = log(@ChlRatio)

set @lnTime = log(10)

-- Secondary calculations
set @u = @ac + (@ad * @Sex) + (@ae * @lnAge) + (@af * @lnAge * @lnAge) +
(@ag * @Sex * @lnAge) + (@ah * @Sex * @lnAge * @lnAge) + (@ai * @lnSystolicBP)+
(@aj * @Smoker) + (@ak * @lnChlRatio) + (@al * @Diabetes) + (@am * @Diabetes *
@Sex) + (@an * @LVH)

if @Sex = 0
    set @mu = @u + (@ao * @LVH)
else
    set @mu = @u

set @ro = exp(@aa + (@ab * @mu))

-- Calculate result
set @risk = 1 - exp(-1 * exp((@lnTime - @mu)/@ro))

return (@risk)

end

GO
```

21.2.06

Dear Dr ..... and partners,

**The e-Nudge Trial**

We are writing to invite you to take part in a new research project involving the University of Warwick and South Warwickshire PCT.

In outline, **the study will involve alert messages and repeated computer searches to identify individuals at high cardiovascular risk**, particularly those who have modifiable risk factors such as raised blood pressure or cholesterol levels. We will also be identifying patients with undiagnosed diabetes based on past raised blood glucose readings. **Further information is included in the enclosed information sheet.**

The trial will investigate whether the repeated flagging up of high risk patients to practice teams reduces the incidence of cardiovascular events (such as strokes, myocardial infarction, or new diagnoses of angina), the number of high risk patients in the population, and the number of patients with undiagnosed diabetes.

**Advantages to your practice** in taking part in this study include:

1. Patients at high cardiovascular risk will be flagged up automatically, **helping you treat them more effectively.**
2. Patients whose hypertension is only evident in the light of their overall cardiovascular risk will be identified, **improving the quality of your hypertension registers.**
3. Patients with **undiagnosed diabetes** will also be identified.
4. In order to accurately measure cardiovascular event rates, we will need to ensure that such events are not double counted (as may happen if two entries are made for the same event), or unrecorded (as may happen in the case of a sudden death). We are therefore offering to carry out these **data quality improvement activities** on your behalf.

All local practices running EMIS LV software will have the opportunity to take part. The searches will be run every eight weeks for two years, and the information will be fed back to each practice through the automatic creation of alert messages. This project is designed under strict confidentiality guidelines. No patient identifiable information will leave the NHS.

**If you are willing to take part, or would simply like some more information please express an interest by returning the attached sheet in the enclosed S.A.E. We will then arrange to contact you personally to provide more details.**

Yours sincerely,

Dr Tim Holt FRCGP    Professor Margaret Thorogood PhD FFPH  
Clinical Lecturer    Chair of Epidemiology

I am interested in taking part in the e-Nudge Trial and would like further information

Practice name: .....

Practice contact:.....

Please return this slip to the research team in the enclosed S.A.E to

Dr Tim Holt  
Centre for Primary Health Care Studies  
Warwick Medical School  
Gibbet Hill Rd  
Coventry CV4 7AL

## The e-Nudge trial: letter of agreement

Name of Practice:.....

Name of practice contact (may be Practice Manager or administrative staff member).....

Email address of practice contact:.....

This letter of agreement must be signed below **by a GP principal** on behalf of the practice, and by a member of the Research team.

**I have read the 'Information for Participating Practices' leaflet and consent to the practice taking part in the e-Nudge Trial. I understand that:**

- **Software will be installed by EMIS for the trial, to create alert messages for high cardiovascular risk patients, at no cost to the practice**
- **The practice will receive lists of high risk patients every eight weeks for two years**
- **A study-funded Research Nurse may need to perform data quality improvement activities in liaison with the practice**
- **The data downloaded for analysis will be entirely anonymous, and used only for the purposes of the study**
- **Practices will not be individually identified in any report or publication**
- **The practice may withdraw from the trial at any time without giving a reason**

Signed for the practice (must be a GP principal):.....

Name:.....

Date:.....

Signed (for the research team):.....

Name:.....

Date.....

Please return this form in the enclosed SAE to: **Dr Tim Holt, Clinical Lecturer, Centre for Primary Health Care Studies, University of Warwick, Coventry CV4 7AL**. Once the form has been signed by the research team you will be sent a copy for your records.





# Using the e-Nudge

A brief guide for participating practices

Dr Tim Holt  
Centre for Primary Health Care Studies  
Health Sciences Research Institute  
Warwick Medical School  
Gibbet Hill Rd  
Coventry CV4 7AL

[tim.holt@warwick.ac.uk](mailto:tim.holt@warwick.ac.uk)

**Warwick**  
Medical School

## Contents

### Using the e-Nudge

What the e-Nudge <i>is</i>	1
What the e-Nudge <i>is not</i>	1

### Frequently asked questions:

How accurate is the e-Nudge?	2
What are the ‘six groups’ that the e-Nudge identifies?	2
How is risk estimated?	3
What should I do if an ‘e-Nudge’ alert appears on the screen?	3
After I have entered new data in a patient’s record, will the e-Nudge alert change immediately?	3
What should I do about the eight-weekly search lists?	3
Why are the patients ‘randomised’?	3
Why have the individual patients not been consented?	3
What information is given to patients about this trial?	4
An alert message mentioned that ‘diabetes status needs clarifying.’ What does this mean?	4
An alert message stated that the patient ‘may have undiagnosed diabetes.’ What should I do?	4
What should I do if an alert keeps appearing, even though I’ve decided that I am not going to do anything about the patient’s risk?	4
<b>Contact details for the research team</b>	<b>5</b>

## Using the e-Nudge

This guide should help you to deal with any problems encountered whilst using the e-Nudge. The software has been designed to be as user-friendly as possible, but there are one or two questions you may have that are answered below.

### What the e-Nudge *is*

The e-Nudge is a system of feedback through which patients at high risk of cardiovascular disease (CVD) are “flagged up” to the practice team. This happens in two ways: through the creation of **alert messages** when the notes of such patients are opened, and through a system of **searches** run every eight weeks.

### What the e-Nudge *is not*

The e-Nudge *assists* in the identification of high risk individuals. It does not give specific risk values, but it does identify patients who are very likely to have a high score. It never indicates that a patient is definitely at low risk, as this is not possible with current general practice data. It is not intended to replace clinical judgement.

## Frequently Asked Questions (FAQs)

### How accurate is the e-Nudge?

We have designed the software to make the best possible use of coded information in general practice databases. However, this information is bound to have limitations, and we have erred on the side of under-estimating risk in order that we do not incorrectly label a patient as high risk. The threshold used is 20% cardiovascular (rather than coronary) risk over 10 years, as is currently recommended.

This means that **if a patient is flagged up as high risk, it is very likely that they are indeed at high risk, but if they are not identified, they are not necessarily at low risk.**

If you fail to see an alert for a patient you expect to be at high risk, this might be because:

- They may be a ‘control’ patient, who will not be flagged up in this trial (see below for more). Control patients should continue to receive usual care, including any means of calculating cardiovascular risk that you currently use.
- Their risk may have been underestimated because it is based on their most recent cholesterol or blood pressure values, rather than the values before treatment. If in doubt, use whatever means of calculating cardiovascular risk that you currently use.
- They may be at high risk due to factors not included in the risk equation, such as family history of cardiovascular disease, ethnicity, central obesity, or impaired glucose tolerance.

### What are the ‘six groups’ that the e-Nudge identifies?

The e-Nudge is designed to identify six different groups of patients from within the over-50s in your practice. The first four of these are:

**Group 1:** Those with existing CVD or diabetes, whose blood pressure or cholesterol is out of target for the nGMS contract. As this is already standard practice in the NHS, the control patients will continue to receive this alert system for this particular group.

**Group 2:** Those who do not have CVD or diabetes, and are under 75yrs, who do not have sufficient information to perform a Framingham risk estimate, but who would be at high risk if “assumed” values were inserted for the missing data.

**Group 3:** Those under 75 who *do* have sufficient information for a risk estimate and who appear to be at high risk of CVD.

**Group 4:** Those aged 75 years or over (too old for a Framingham calculation) whose last three consecutive blood pressure readings were all out of the range <160/100 mmHg.

Two further groups are identified, largely to support the quality of the practice’s Diabetes register (recognising that type 2 diabetes may be under-diagnosed):

**Group 5:** Those with possible undiagnosed diabetes, based on at least one past raised blood glucose level  $\geq 11.1$  mmol/L, but no diagnosis of diabetes and no subsequent non-diabetic fasting level or Glucose Tolerance Test appropriately coded.

**Group 6:** Patients with cardiovascular disease (on the CHD or Stroke/TIA registers) but not diabetes, who do not have a blood glucose level recorded in the past 3 years.

### **How is risk estimated?**

Patients in Group 1 are identified in the usual way, using the practice's disease register to identify those with CHD, Stroke/TIA, or Diabetes. For primary prevention patients (who do not already have cardiovascular disease) less than 75 years old, the e-Nudge estimates risk by extracting the most recent values of the Framingham variables and performing a risk calculation using the Framingham cardiovascular risk algorithm. In the case of systolic blood pressure, an average of recent values is taken where available. For Group 3 alerts, the assumptions used by the software are stated, so that you may check they are correct if there is any doubt. For instance, smoking status is not always clear or up to date in a patient's record, so you might like to check that the patient is still a smoker if this has been assumed.

### **What should I do if an 'e-Nudge' alert appears on the screen?**

This is up to you and depends on your clinical judgement. You are not obliged to do anything. The message can be cleared by simply hitting the 'Return' key, as for the usual nGMS alerts.

### **After I have entered new data in a patient's record, will the e-Nudge alert change immediately?**

No. Any action taken in response to the e-Nudge will take up to 24 hrs to be 'noticed' by the software, as the information that the software uses is updated using a search each night on the practice database.

### **What should I do about the eight-weekly search lists?**

It is up to you what you do with the eight-weekly lists. The lists are intended to identify all the patients in the practice who would get an 'alert' message if their notes were opened on the day the search is run. Of course, many of these patients may not present to the practice, and it is up to you whether you contact any of them about this.

### **Why are the patients 'randomised'?**

This is a randomised controlled trial. The practice population is divided randomly into 'control' and 'intervention' patients using an electronic technique. The **control** patients will simply receive the usual care currently in place in the practice, including any means you may be employing to identify and control their cardiovascular risk. The **intervention** patients will be subjected to the e-Nudge, which is the software tool programmed into your computer system for the trial. Over the duration of the trial we will be examining whether the e-Nudge leads to improved control of risk factors and reduced incidence of cardiovascular events such as heart attacks and strokes in the intervention patients compared with the control patients.

### **Why have the individual patients not been consented?**

This trial has been approved by the Warwickshire Local Research Ethics Committee. The committee agreed that the trial's participants are the practitioners involved in caring for the patients, and not the patients themselves. The control population will continue to receive their usual care during the trial. The benefits of e-Nudge alerts have not yet been demonstrated in a primary care based controlled trial, so this randomisation is necessary.

### **What information is given to patients about this trial?**

A poster has been provided by the research team to display in the waiting area if the practice wished to use it. Further copies can be supplied if required. The poster explains that the practice is taking part in a research trial, and provides a contact number for more information if needed. If any patients want to know more about the study, any of the research team listed at the bottom of this document will be happy to talk to them.

### **An alert message mentioned that ‘diabetes status needs clarifying.’ What does this mean?**

The e-Nudge software looks for possible high risk patients who do not have sufficient information recorded to perform a risk estimate. If the patient would get a high Framingham risk estimate using a positive input for diabetes status, *and* there is no blood glucose measurement on record in the past three years, then this patient would be flagged up asking for diabetes status to be clarified. The software will never perform a Framingham calculation on someone who is known to have diabetes as this is no longer recommended practice. The e-Nudge identifies patients likely to benefit from having their diabetes status clarifying – those who would get a high Framingham risk estimate if they did have diabetes and who haven’t been tested recently. To clarify diabetes status in this trial for such patients, all that is needed is a blood glucose measurement of any kind (random or fasting). The method chosen is up to the clinician.

### **An alert message stated that the patient ‘may have undiagnosed diabetes.’ What should I do?**

This means that the patient is not on the diabetes register, but has at least one recorded blood glucose measurement  $\geq 11.1$  mmol/L in the record. The patient may have had further *fasting* glucose levels that are  $\leq 6.9$  mmol/L recorded in the system. However, fasting measurements are often not coded properly due to the way results are returned from the laboratory. In such a patient, all that is needed is to re-insert the fasting level, with the date it was measured, using the Read Code 44g1 and the alert will stop appearing

If a fasting level has not been carried out, then this could be arranged (if you feel it is necessary) and this code applied manually when the result is obtained. Other codes that can stop the alerts from appearing are ‘Oral Glucose Tolerance Test’ (Read code 44V1) or ‘Diabetes resolved’ (Read codes 21263 or 212H).

### **What should I do if an alert keeps appearing, even though I’ve decided that I am not going to do anything about the patient’s risk?**

It may be inappropriate for clinical reasons to address a person’s cardiovascular risk. Like the GMS alerts, the e-Nudge alerts will continue to appear, but you can just clear them by pressing the ‘Return’ key.

## Contact details for the research team

If you or your patients have any further questions or experience any problems during the study, please contact one of the research team listed below.

Dr Tim Holt  
Clinical Lecturer

Email: [tim.holt@warwick.ac.uk](mailto:tim.holt@warwick.ac.uk)  
Tel: 02476 574898 Mobile: 07967 757471  
Fax:: 02476 572950

Professor Margaret Thorogood  
Chair of Epidemiology

Email: [Margaret.thorogood@warwick.ac.uk](mailto:Margaret.thorogood@warwick.ac.uk)  
Tel: 02476 574509

Dr Frances Griffiths  
Senior Clinical Lecturer

Email: [f.e.griffiths@warwick.ac.uk](mailto:f.e.griffiths@warwick.ac.uk)  
Tel: 02476 522534

Health Sciences Research Institute  
Warwick Medical School  
Gibbet Hill Rd,  
Coventry CV4 7AL

Alternatively, you could contact the Research Office and speak to Mrs Krysia Saul (email: [krysia.saul@warwick.ac.uk](mailto:krysia.saul@warwick.ac.uk)) or tel: 02476 573163.

## **e-Nudge lists: Eight weekly reminder**

Dear colleague,

This is your eight-weekly reminder that the e-Nudge lists are available. Please acknowledge receipt of this email by simply 'replying to sender.'

The lists can be accessed any time as follows:

Main Menu

ST – Search and Statistics

B – Patient searches

S – Search results

Scroll down to find the 'e-Nudge intervention populations' and press Return.

To remind you, there are six groups identified:

**Group 1:** Patients with cardiovascular disease (CVD) or diabetes, whose blood pressure or cholesterol is out of target for the GMS contract.

**Group 2:** Patients without CVD or diabetes, who do not have sufficient information for a Framingham risk estimate, but who would be at high risk if "assumed" values were inserted for the missing information.

**Group 3:** Patients under 75 who do have sufficient information for a risk estimate and who appear to be at high risk of CVD.

**Group 4:** Patients over 75 years (too old for a risk calculation) whose last three blood pressure readings were all out of the range <160/100 mmHg.

**(Group 5:** Patients with possible undiagnosed diabetes - this group has been withdrawn from the trial as of November 2006 as new EMIS software will be performing a very similar function on all patients in the practice.)

**Group 6:** Patients with cardiovascular disease but not diabetes, who do not have a blood glucose level recorded in the past 3 years.

If you are unclear about this then please refer to the User Guide, or contact me (contact details below).

Best wishes,

Tim Holt

## The e-Nudge Trial – Data collection for the DMC

### Introduction

These notes describe a protocol for cleansing and extraction of data for the e-Nudge Trial Data Monitoring Committee.

The e-Nudge Trial tests the effectiveness of a software tool (e-Nudge) that identifies (and regularly updates) lists of patients at risk of cardiovascular disease, and flags them up to the practice teams. It operates only on those over-50 years, and randomises the population into ‘control’ and ‘intervention’ patients. Only the intervention patients are alerted. The control patients continue to get ‘usual care.’

The Data Monitoring Committee needs to examine the difference in the rate of cardiovascular events in the control and intervention arms. If it were greater than 20%, the trial would need to be stopped.

A *cardiovascular event* is defined as any of the following:

- A new diagnosis of ischaemic heart disease
- A new diagnosis of cerebrovascular disease
- A myocardial infarction (patient may already be known to have ischaemic heart disease)
- A stroke (patient may already have cerebrovascular disease eg past stroke or TIA)
- A Transient Ischaemic Attack (TIA) (patient may already have cerebrovascular disease)
- Sudden death from cardiovascular disease

An entry of ‘Angina’ in someone who is already known to have IHD is not a new event unless it is associated with admission for a coronary artery procedure e.g. angioplasty. However it *is* a new event if it occurs in someone who did *not* already have diagnosed IHD.

Sudden cardiovascular deaths are not always recorded electronically, but we decided that as it is usual practice to make such a record, we will assume for this exercise that the searches will pick up the majority of these events.

### Constructing the searches

The searches should identify patients who have had an event during the first 12 months of participation in the study. This date range needs to be applied to the search protocol as below. From the EMIS Main Menu:

- ST** Search and Statistics
- B** Patient searches
- A** Add a new search

**Search population:** All patients in the database (**including** those who have died or left the practice)

**Add a feature:** Age - Upper limit 120 years, lower limit 50 years

**Add a feature:** G3 Ischaemic Heart Disease (Add date range)  
Include all children codes including Acute Myocardial Infarction G30

**Add a feature:** G6 Cerebrovascular disease (Add date range)  
Include all children codes



Press **Return** when complete, and name the search, mentioning 'e-Nudge' in the name, and filing it in the 'One off searches' folder.

### **Run** the search

Access the search results by 'View to Screen,' to produce a list of names and EMIS numbers.

Print the list out (and make sure the print out is kept securely in the practice when the exercise is finished).

For each patient on the list, do the following in this order:

1. Check date of registration of the patient with the practice
2. Access the Medical Record to examine and count each event
3. Record the last digit of the NHS Number

The date of registration with the practice is noted in the **Registration Status** module (**RS** from the Main Menu).

If the date of registration is close to (eg within 4 months of) the date of commencing the trial then it is important to confirm that the event was a true event occurring at that time, rather than an entry referring to a past event entered when the patient was first seen at the practice before the past notes had arrived, as may happen during a New Registration Check.

### **To access the Medical Record:**

From the EMIS Main Menu:

- MR** Medical Record
- X** All Non-Values
- O** Codes on/off

This reveals the codes of all the entries. Scroll down to identify the date range of interest, and find the cardiovascular event codes (which will begin with G).

Then look into the Consultation record (press C from the Medical Record screen) and scroll through the 12 month date interval to check the events. Record how many new events occurred during this time for each patient. In most cases there will probably be only one. **Note:** there may be some events in the Consultation record that are not in the 'All Non-Values' list, and vice versa.

Finally, access the **Registration Details (RD)** to find the NHS number, and note the last digit.

The lists of patients identified should be left in a secure place in the practice, so that they could be retrieved later if needed.

The only **information to be removed from the practice** is:

- Name or site number of practice
- Number of patients identified
- Number of events for each patient
- Last digit of NHS number for each *event*

Paper title (First author and year)	
Reviewer	
Country	
Subjects (describe)	
Setting	
Unit of randomisation and randomisation method	
Describe intervention	
Describe control condition	
Outcome measure time	
Outcome measures (type)	
Were any outcome measures quality checked?	
Rate of follow-up	
Number of subjects randomised	
Number of subjects in final analysis	

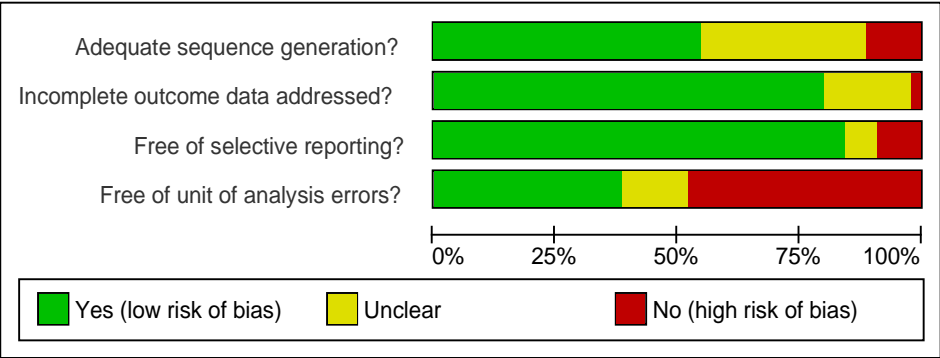
First outcome measure (describe):

	Control	Intervention 1	Intervention 2	Intervention 3
Baseline numerator and denominator (if given)				
Outcome numerator and denominator				

Second outcome measure (describe):

	Control	Intervention 1	Intervention 2	Intervention 3
Baseline numerator and denominator (if given)				
Outcome numerator and denominator				

	Adequate sequence generation?	Incomplete outcome data addressed?	Free of selective reporting?	Free of unit of analysis errors?
Bates 1999	+	+	+	+
Burack 1996	+	+	?	+
Burack 1998	+	+	?	+
Chambers 1991	+	-	+	-
Dexter (1) 1998	?	?	-	-
Dexter (2) 1998	?	?	-	-
Dexter (3) 1998	?	?	-	-
Dexter 2001	+	+	+	-
Filippi 2003	?	+	+	-
Frank 2004	+	+	+	+
Hicks 2007	?	+	+	-
Judge 2006	-	?	+	-
Kenealy 2005	+	+	+	-
Kralj 2003	-	?	?	+
Krall 2004	?	?	+	+
Kucher 2005	+	?	+	+
Litzelman 1993	?	+	+	+
Lo 2009	?	+	+	-
Matheny 2008	?	+	+	-
McCowan 2001	+	+	+	+
McDonald 1976	+	+	+	?
McDonald 1980	?	+	+	+
McDowell 1989a	-	+	+	-
McDowell 1989b	?	+	+	+
Murray 2004	+	+	+	-
Overhage 1996	?	+	+	?
Overhage 1997	?	+	+	?
Rosser 1991	+	+	+	-
Rosser 1992	+	+	+	-
Rossi 1997	+	+	+	-
Rothschild 2007	+	+	+	-
Safran 1995	-	+	+	?
Sequist 2005	-	+	+	-
Shea 1995	+	+	-	+
Tamblyn 2003 (Discon)	+	+	+	+
Tamblyn 2003 (Pres)	+	+	+	+
Tamblyn 2008	+	+	+	+
Tape 1993	?	+	+	-
Tierney 1987	+	+	+	+
Tierney 2003	+	+	+	?
Tierney 2005	?	+	+	?
van Wijk 2008 (Screening)	+	+	+	-
van Wijk 2008 (Treatment)	+	?	+	-
White 1984	+	+	+	+



Risk of bias tables for systematic review (Chapter 4)

Practice's headed paper

Name  
Address

Dear .....,

Our practice is taking part in a research trial based at the University of Warwick. The research is about the prevention of heart disease and strokes using computers in the practice. The University researchers are interested to know what patients think about how these conditions should be prevented, and they would like to interview you as part of this project.

We are enclosing an Information Leaflet about the study, which you should read before deciding. It gives details about the study, and who to contact if you need further information.

If you agree to take part, please complete the slip below and return it to the University in the FREEPOST envelope enclosed. The research team will then get in touch with you to arrange a date and time to meet up for an interview.

**There is no obligation to take part in this study. If you prefer not to take part then this will not affect your medical care in any way.**

Yours sincerely

The practice

-----

**I am interested in taking part in the research study**

**I would like further information before deciding**

My name is:.....

Telephone number:.....

Or Email address:.....

Signed.....

Date.....

Please send in the FREEPOST envelope to: Dr Tim Holt, Health Sciences Research Institute, Warwick Medical School, Gibbet Hill Rd, Coventry CV4 7AL.

## PATIENT INFORMATION SHEET

### **Patients' views of the use of information technology in reducing the risk of cardiovascular disease**

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

#### **What is the purpose of the study?**

Preventing heart attacks and strokes ('cardiovascular disease') is an important part of the work of a general practice. For some people, changing their lifestyle or taking medication to reduce their risk is important, whilst for others it is much less so. We are interested to find out more about patients' attitudes towards this, and also whether they feel computers can help their doctors to identify those at highest risk.

#### **Why have I been chosen?**

Your practice is taking part in a research trial that is testing a software tool for identifying patients at risk of heart disease and stroke. As part of this research it is important for us to understand the attitudes of patients in the practice. Your name has been selected **randomly** from those over 50 years old in the practice. This invitation to participate does **not** mean that you have been identified as high risk.

#### **Do I have to take part?**

No. You are perfectly entitled to decline the invitation to participate, or to withdraw from the study at any time without giving a reason. If you do, you will be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

#### **What will happen to me if I take part?**

If you agree to take part, you will be contacted by the research team either by telephone, or by email, whichever you prefer, to arrange a time and place for the interview that suits you. This could be in your own home, at the University of Warwick, or at another location if you prefer. We would pay your travel expenses if it is not in your own home. If you are happy to proceed you will be asked to sign a consent form. The researcher will then ask you some questions, and encourage you to talk about your attitudes towards avoiding heart disease and strokes. The interview will last approximately one hour and will be audio recorded. The interview will be 'transcribed.' All the personal identification will be removed during transcription. After the interview you can still withdraw your consent.

#### **What are the possible advantages, disadvantages or risks of taking part?**

We cannot promise the study will help you but the information we get might help improve the treatment of people with cardiovascular disease. We do not believe there are any significant risks in taking part. Whether or not you decide to take part will not affect your medical treatment in any way.

#### **What if there is a problem?**

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, complaints procedures will be maintained for which the Chief Investigator takes responsibility. Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Please contact:

Professor Yvonne Carter  
Dean  
Warwick Medical School  
Gibbet Hill Rd  
Coventry CV4 7AL  
Telephone: 02476 574509

**Will my taking part in the study be kept confidential?**

Yes. All the information about your participation in this study will be kept confidential to the research team.

**Contact Details:**

The research team are:

Dr Tim Holt, Clinical Lecturer  
Professor Margaret Thorogood, Professor of Epidemiology  
Dr Frances Griffiths, Senior Clinical Lecturer

Health Sciences Research Institute  
Warwick Medical School  
Gibbet Hill Rd  
Coventry CV4 7AL

and Dr Stephen Munday  
Director of Public Health  
South Warwickshire Primary Care Trust

**For further information about the study, please contact:**

Dr Tim Holt  
Warwick Medical School  
Gibbet Hill Rd  
Coventry CV4 7AL  
Telephone: 02476 574898 or 02476 572950

**What will happen to the results of the research study?**

The information we gather during the interviews will be analysed, and the results will be published in medical journals and through conference presentations. You will not be identified in any of these reports, articles or presentations.

**Who is organising and funding the research?**

This study is sponsored by the University of Warwick, and funded through a Department of Health PhD studentship. The research team receives no payments for including you in the research project.

**Who has reviewed the study?**

This study was given a favourable ethical opinion by the Warwickshire Local Research Ethics Committee.

**Thank you for taking the time to read this sheet, and for considering taking part in this study.**





## **Interviews with members of the public**

The following pages describe a series of in-depth interviews with members of the public that I undertook as part of a process evaluation in support of the e-Nudge trial. Ethical approval for this study was gained from Warwickshire Local Research Ethics Committee.

### **Selection of patients**

I recruited a practice in Stratford upon Avon that was taking part in the e-Nudge trial, to provide access to individuals to invite for interview. I visited the practice and asked the manager to print out the computer record numbers of individuals in three different age categories (50-65, 65-75, and over 75). I then randomly selected a sample of 30 record numbers (ten from each age band). The GPs then checked the records of all 30 and excluded three. The final list of 27 patients were invited by the practice by letter on practice headed paper with a tear off slip suggesting that they contact me directly if interested. Nine responded, and of these eight were interviewed. In the ninth case a suitable arrangement could not be identified.

I considered the option of recruiting people that had been identified on the e-Nudge lists (e.g. those with raised CVD risk) as their opinions might be more relevant than those of the low CVD risk population. But I felt that it was important (as the interviewer who might have to explain this) that I could assure each participant that they had been identified at random, and that their invitation did not imply anything about their own CVD risk. This was an important part of reassuring them that I had not examined their records without their consent.

Nine people responded, and in eight cases I was able to make a satisfactory arrangement to meet up. I spoke to the ninth individual by phone but he did not subsequently get back to me as agreed, so after failing to contact him again I did not continue. The interviews were conducted at a venue of the interviewee's choice, which

was the individual's home in all but one case (the preliminary pilot interview that occurred at the University of Warwick). The Patient information sheet and Patient consent form are also given in the Appendix.

### **Topic guide**

The topic guide was as follows:

- Patients' general perceptions of the value of prevention (rather than treatment) for cardiovascular disease
- The perceived roles of lifestyle intervention, and of drug therapy in prevention
- What, if any, is their individual experience of preventive therapy for cardiovascular disease?
- How does this issue compare with other priorities in their life?
- Whether they welcome the use of information technology to clarify their individual risk
- Whether they feel this should be left largely to the health professional's clinical skill.

### **Thematic analysis**

The interviews were audio-taped and sent to a professional secretarial service for transcription. I then examined the transcripts and highlighted each statement of particular relevance in the text with a marker pen. After examining the first two interviews I identified a number of themes and gave each a definition, according to its inferred meaning, using a basic thematic analytical approach (1). Further interviews were then analysed and the same themes were highlighted. New themes were also recognised, leading to a re-examination of the previous transcripts to seek these previously unrecognised themes within them. In some cases the meaning of the

statement was within the definition of an existing theme and did not require the creation of a new theme, but did require a broadening of its definition.

At the end of this iterative process I had constructed a grid listing the themes and providing definitions, any variation in usage or meaning, and examples. This is given in Table 1.

Theme label	Definition and variation in inferred usage	Examples from transcripts (patient number in brackets)
Lifestyle	Lifestyle factors (not requiring any measurement by the medical profession) mentioned as relevant to cardiovascular risk, e.g. diet, exercise, weight.	<p>“We try to eat sensibly as much as we can and we do take quite a lot of exercise.” (4)</p> <p>“..he [father] was very careful about his diet. He wouldn’t have any fat or anything. And so he slimmed himself right down.” (7)</p>
Genes	Genes mentioned as relevant to cardiovascular risk. Familial factors including non-genetically determined behaviours clustering within families included.	<p>“I come from a thin family..” (5)</p> <p>“..its in your genes I suppose.” (7)</p>
Other risk factors	Cholesterol, blood pressure and other factors that usually require the medical profession to measure are relevant to cardiovascular risk	<p>“...but if there was evidence that that [future blood clot] is possible because obviously my cholesterol is high or whatever...” (8)</p>
Social factors	Respondent mentions other, social factors possibly relevant to CVD risk, such as environmental exposure to fumes, stress, etc	<p>“..emissions from power plants and incinerators..”</p> <p>“Because he [father] had an office job...he had early retirement.” (7)</p>
Choice	Individuals should be allowed to choose the extent to which they accept lifestyle advice, drug therapy, or risk assessment.	<p>“At the end of the day it’s their choice and they know darn well that if they carry on smoking they’re possibly at higher risk of dying before someone who doesn’t smoke.” (3)</p> <p>“But if you invited people, and they had a choice of whether to come in or not, it would be their decision wouldn’t it?” (4)</p>
Personal responsibility	Individuals have a responsibility to look after their own health (usually this means through lifestyle). Extended to include the responsibility of parents to establish healthy lifestyle patterns in children	<p>“On obesity that is completely up to you, if you are obese the only way is obviously food, drinks, whatever the case may be, so that is up to you.” (8)</p> <p>“It’s difficult to know about diet, what causes it, whether it’s the home life which should be changed, what the parents feed their children on, what the children eat.” (6)</p>

<p>Health service responsibility</p>	<p>Health care providers have a responsibility (either to individuals or to society) to address the problem of CVD prevention</p>	<p>“It’s the medical professions [responsibility] to sort of suggest that they stop smoking or they cut down or get slimmer” (6)  “I feel that not enough effort is put into it [into prevention by the medical profession], and, as I said, I find it very disappointing.” (8)</p>
<p>Positive about prevention</p>	<p>Respondent feels positive about the preventive approach, but it was not compared specifically with a treatment/curative approach</p>	<p>“Anything you can do to predict that there is a potential problem coming up I’m in favour of, because you can then start doing something to avoid that problem...I’m 100% behind it” (1)  “I suppose if I can I’d rather prevent something” (3)</p>
<p>Negative about prevention</p>	<p>Without necessarily comparing it to ‘cure,’ the respondent makes a negative comment about the preventive approach in general.</p>	<p>“Well I don’t think that’s essential, definitely don’t.” (2)  “..you see they don’t give people with cancer all the treatment they should want ... and I think that they’ve already got it and I don’t see why money should be spent on people who don’t change their lifestyle, ... as against the people who are ill. Seriously ill.” (6)  “..supposing someone examines me and everything is in perfect order and there is no history of whatever, why should I take I suppose aspirins to thin the blood..” (8)</p>
<p>Prevention is better than cure</p>	<p>A preventive approach (health service or individual) is preferable to an approach based on treating or curing established conditions.</p>	<p>“Oh I’d rather, preventative is much better than cure isn’t it,” (2)  “Because in the end, its better to prevent things happening than cure them when they have happened.” (4)  “It might be worth spending a lot of money on a lot of</p>

		<p>people, to prevent even one person having that [quadruple bypass] in terms of cost.” (5)  “Alright you can treat or try to cure it as much as you can, but prevention I think is much better..” (8)</p>
Element of chance	Unpredictable factors are involved in determining cardiovascular disease outcomes	<p>“I suppose nobody knows really when one’s [heart attack] going to strike.” (3)  “Its in the lap of the gods isn’t it” (6)</p>
Medical authority	The medical profession is more influential than lay sources in advising or managing cardiovascular risk, either through its professional status or its ability to offer personalised rather than population level advice or treatments.	<p>“So I feel I’m in his hands really [the doctor’s], and if he suggests something I go ahead with it.” (4)  “Oh, I certainly wouldn’t allow somebody who’s not from a medical background to influence me like that.” (2)  “I think people are far more likely to take notice of their doctor than a programme on the telly.” (6)</p>
Lay sources	Information or advice originating from lay (non-health professional) sources mentioned in either a positive or negative light	<p>“...if you read the paper every day, magazines, its there all the time, about diet...” (5)</p>
Preventive drug therapy less preferable	Preventive drug therapy is less preferable than lifestyle change in reducing cardiovascular risk	<p>“Well if you say to them ‘stop smoking’ and they don’t.... Well I don’t think you should give them any drugs then.” (7)  “and if that wasn’t possible for whatever reason, then obviously I would resort to tablets...” (8)</p>
Other serious disease	Other diseases (such as cancer or dementia) compared with cardiovascular disease as a serious health concern	<p>“I think I would worry more about losing my mental ability.” (6)  “My mother died of breast cancer, alright I went to the doctor and asked what my chances were and if anything could be done.” (6)</p>
Silent disease	Disease may be established at an asymptomatic stage, at which point it might be amenable to preventive therapy.	<p>“I don’t really know if there is something wrong with me or not....” (8)</p>

Adequacy of records	Respondent aware that information in practice records might help to predict CVD risk, whether or not they can comment on their adequacy.	“If that doesn’t give them enough information for them...to work out whether I’m prone to whatever, I think it’s a very poor show basically.” (8)
Stigma inappropriate	Any stigma attached to the label ‘At risk of CVD’ (e.g. effect of the label on self image or life insurance risk, etc) is inappropriate or unfair	“..the insurance company would have to accept that somebody with a 20% risk of heart disease, is not somebody that they shouldn’t cover.” (5)
Stigma appropriate	Stigma attached to the label ‘At risk of CVD’ is a relevant and understandable concern	“..you wouldn’t want to be turned down for insurance, would you?” (4) “You know, its putting a stigma on people, isn’t it” [referring to insurance implications] (6)
Age factors <i>T</i>	Use of a person’s age (rightly or wrongly) to influence the management of their CVD risk, or more generally the relevance of age to the whole process of CVD prevention.	“I certainly take more notice now I’m my age 60, just over 60.” (3) “I’m 67 at the moment, when I’m 77 I’ll probably have a different attitude to it.” (5) “I would be grateful for any help because at my age I think I’m on borrowed time now myself.” (7)
Side effects	Side effects of medication are discussed as a possible negative aspect of prevention.	“..there’s always a side effect of some kind with any drug.” (4)

*Table 1: Recurring themes in the in-depth interviews with members of the public.*

Theme label	Interviewee number							
	1	2	3	4	5	6	7	8
Lifestyle	6	3	4	3	1	6	8	2
Genes	4		2	3	3	1	2	1
Other risk factors	3	1	1	1	1	1		2
Social factors	1	1			1		1	
Choice			4	1	2	3		4
Personal responsibility	2	1	3			4		5
Health service responsibility	1	1				1		5
Positive about prevention	2	4	7	5	4	5	4	1
Negative about prevention		4				1		
Prevention is better than cure	1	1	2	1	3			1
Element of chance			1	1		1	2	1
Medical authority	2	5	2	2	3	3	2	1
Lay sources					5			
Preventive drug therapy less preferable		3		1		3	2	6
Other serious disease			1		1	4		2
Silent disease				1				1
Adequacy of records	3	1	4	1	5	1	1	1
Stigma inappropriate	3		3	1	2	1		1
Stigma appropriate	1		1	3	1	1		1
Age factors	1		3		2	1	1	2
Side effects			1	1	1		1	

*Table 2: Frequency of recurring themes in the eight interviews with members of the public.*



## **Emergent themes**

The recurring themes were generally expected and the Topic guide was designed to explore these areas, although I took care to ensure that they arose spontaneously. An interesting outcome was that an individual might display conflicting views during the same interview.

A number of other themes and issues emerged from the data and were less expected:

1. Value of bypassing the medical profession for information or advice, e.g. through the Internet. This was suggested by the first interviewee, and also by the fifth.

2. The value of receiving written confirmation of risk. “There’s nothing like a written warning, verbal warnings don’t count.” This was stated by the first interviewee, to support the systematic (rather than opportunistic) approach that would involve invitations to attend for clarification of risk.

3. The same interviewee was also concerned about the risk algorithm and its adequacy, rather than just the adequacy of electronic information to support it.

4. Two interviewees (2 and 7) felt that a preventive approach would indicate that the practice cared about or was interested in them, as they would be going out of their way to safeguard their future health.

5. Perceived vulnerability, whilst not used explicitly as a term, was a concept brought up by at least two interviewees (3 and 7), who recognised that people vary in their own self-perceived resilience to lifestyle factors and to the less predictable elements of CVD risk.

6. Interviewees 3, 4 and 8 mentioned governmental resource implications of CVD risk reduction, i.e. the costs of preventive health care.

7. A ‘Big Brother’ reference by interviewee 2 was similar to a comment by interviewee 5 about the authorities forcing people to change their lifestyle.

8. Finally, a preference for sudden death (over lingering dependence) was expressed by two interviewees: “So I’d rather go out like a candle than be bloody

lingering for a couple of years” (Interviewee No 7). The other one was a comment that I noted by hand after the audiotape recorder had been switched off: “The best solution would be to wait until you get the Alzheimer’s disease, and then have the heart attack!” (Interviewee No 8). I had not included this area in the Topic guide, and so did not feel that I had ethical approval to explore what was probably a very emotive issue particularly in the older age groups.

### **Summary of the analysis**

Having analysed the interview transcripts, I arrived at the following conclusions over the opinions and beliefs of the participants:

- The participants generally believed CVD prevention to be an important and valuable area of health care.
- Lifestyle issues (such as diet and exercise) were given as examples of CVD risk factors rather than those that the medical profession might identify as priorities, such as blood pressure, blood glucose, and cholesterol.
- The interviewees generally considered that attention to lifestyle factors (and not just those amenable to drug therapy) was within the remit and responsibility of the medical profession. They generally felt that lifestyle factors should be addressed before considering drug therapy.
- Regarding electronic data, there was little awareness of what exactly is recorded and the importance of the distinction between electronic data and free text data when it comes to identifying at risk individuals.
- Most interviewees thought that identifiable individuals at risk of CVD should be made aware and should be helped to take action over it. Electronic means of assisting with identification were generally welcome.

- Potentially negative aspects of CVD prevention arose during several of the interviews. Side effects of medication were mentioned by four interviewees, in two cases without me raising the issue. The potential problems of ‘labelling’ individuals at risk were recognised, but generally only when I raised them. This issue was not actually included in the Topic guide but arose during the interviews. This was related to the phenomenon of ‘turning people into patients’ discussed in Chapter 3, and I was a little surprised that it did not provoke more spontaneous comment than it in fact did.

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# A nationwide adaptive prediction tool for coronary heart disease prevention

Tim A Holt and Lucila Ohno-Machado

## SUMMARY

*Standardised electronic recording of cardiovascular risk factor data collected during primary care delivery could be used to create a new strategy, using an adaptive prediction model, for targeting primary prevention interventions at high-risk individuals. In the short term, this should progressively improve data quality and allow risk modification to be monitored at the population level. In the long term, feedback of data on cardiovascular disease development might enable the model to tailor the recommended interventions more appropriately to the needs of the individual and to adapt to future changes in risk patterns. Ultimately, the inclusion of additional cardiovascular risk factors might enable a richer, more realistic picture of cardiovascular risk profiles to be uncovered. This model may have wider uses in both research and practice, and provides a further incentive for the standardisation of record keeping in primary care.*

**Keywords:** *primary prevention; number needed to screen; coronary heart disease; adaptive learning.*

## Introduction

THE National Service Framework (NSF) for coronary heart disease<sup>1</sup> recommends that patients with a greater than 30% risk of developing coronary heart disease in the following 10 years should be treated with a similar priority to those with established disease. Identifying such patients, who lack cardiovascular symptoms, presents a challenge for primary care teams, and the NSF stresses the need for a systematic rather than opportunistic service model, using electronic disease registers and standardised Read codes. There have been doubts about the quality and reliability of data collected in primary care ever since the development of large computer databases during the 1980s,<sup>2</sup> but where coding can be standardised, the ability of existing software, such as MIQUEST, to extract the data anonymously from practice databases provides the opportunity for a nationwide data collection system. Such standardisation is becoming an important means through which the goals of the NSF can be achieved.<sup>3</sup> Patterns of cardiovascular risk among the United Kingdom (UK) population may vary in this century, as they did in the last, through changes in demography, lifestyle patterns, social conditions, modification of risk factors, and through genetic exchange with populations not adequately represented in the Framingham study,<sup>4</sup> the data source on which current predictions are based. In this paper we discuss how an adaptive model might facilitate the identification of high-risk patients, progressively improve data quality, and ultimately adapt to the needs of individuals in a situation of changing coronary heart disease risk.

## Adaptive predictive models

Adaptive predictive models are capable of 'learning' to classify cases according to patterns. They use existing data and classification 'gold standards' to construct a model that can predict to which class a new case belongs. They include algorithms, such as logistic regression, which was the basis for the Framingham algorithm, as well as more complex models, such as neural networks,<sup>5</sup> support vector machines,<sup>6</sup> and classification and regression trees.<sup>7</sup> Neural networks, which are widely used in industry for pattern recognition and quality control, comprise input and output layers of processing units, between which hidden layers modify the transmission of information by attributing 'weights' to the various patterns of incoming data. Successful pattern recognition is reinforced through an increase in the weight attributed to the relevant input pattern. This is done initially by 'training' the network using an existing database, and then (if necessary) allowing the relative accuracy of future predictions to adjust the weighting mechanism in the hidden layers (Box 1).

T A Holt, MRCP, FRCGP, Member, Complexity in Primary Care Group and general practitioner, Whitby. L Ohno-Machado, PhD, MD, Associate Professor of Radiology, Health Sciences and Technology, Decision Systems Group, Brigham and Women's Hospital, Harvard Medical School and Massachusetts Institute of Technology, Boston, MA.

### Address for correspondence

Dr Tim Holt, Dale End Surgery, Danby, Whitby, North Yorkshire YO21 2JE. E-mail: tholt@ukonline.co.uk

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A neural network might be used as a quality control device in a plate factory. The inputs would include features of the plate, such as its thickness, reflectivity and shape, and the output would be a prediction of how easily it might break.

The relative success of the predictions (determined by the rate of plate breakage) could be allowed to modify the weights given to the appropriate input patterns, so that the network effectively 'learns' from experience, and can adapt its predictions over time to consistent changes in the environment to which the plates are exposed.

Box 1. An example of a neural network.

Baxt has described a neural network model used to interpret patterns of symptoms, clinical signs, and electrocardiograph findings in 356 patients presenting with acute chest pain to a hospital emergency department, 120 of whom were subsequently found to have myocardial infarction.<sup>8</sup> Twenty input variables for each patient were fed in to the network, which was trained using the data from half the patients and then tested on the other half. The training and testing was then repeated using the opposite halves of the sample. The network was able to recognise the patients with myocardial infarction with greater success than either physicians or previous computer-based strategies. By recognising the significance of combinations of minor variables, it performed well even in the absence of electrocardiographic signs of infarction. A neural network model has also been used successfully to assess cardiovascular risk using a number of different lipids as input variables.<sup>9</sup>

If data collected during the process of care is used to build an adaptive prediction tool, it will be more likely that the model will perform well in classifying new cases. Data collected in more controlled environments may be more adequate to characterise risk factors and classify new cases in a similar population than to classify new cases in a different population. The Framingham algorithm has been validated in northern Europeans,<sup>10</sup> but may not remain valid indefinitely, and is not universally applicable to all ethnic groups without recalibration.<sup>11</sup>

One of the strengths of collecting electronic data during the process of care is that large sets of data can be collected in a relatively short time. Taking advantage of this to construct adaptive models that will be used in a similar population is very important. Another benefit is that different models can be constructed in which only certain variables need to have corresponding values. For example, in the electronic implementations of the Framingham algorithm suggested by the NSF,<sup>12</sup> the software will not produce a risk estimate unless all the variables have corresponding values. If the value for HDL cholesterol is unknown, for example, the algorithm either assumes an estimated value or it will not run. Adaptive predictive models built with a subset of the variables could be used in these cases. This ability makes such models useful in the presence of incomplete data, and would become important if additional risk variables were to be included in the calculation in the future.

### Current primary prevention strategies

'Ten-year risk' is currently assessed using the Framingham algorithm and the individual patient's risk variables (Box 2).

- Age
- Sex
- Smoking status
- Systolic blood pressure
- Total serum cholesterol level
- Serum HDL cholesterol level
- Presence or absence of diabetes
- Presence or absence of left ventricular hypertrophy

Box 2. The Framingham input variables.

These variables were selected for the Framingham study because they are 'objective and strongly and independently related to CHD'.<sup>13</sup> Other factors known to affect risk include the patient's ethnic group, exercise level, alcohol consumption, other dietary variables, family history, body mass index, and waist-to-hip ratio. The exclusion of these factors limits the accuracy of the Framingham calculation, but in an individual's case can be used to modify risk estimations at the discretion of the clinician.<sup>14</sup> How much to adjust remains an open issue.

The NSF recommends that patients known to have hypertension and/or diabetes are selected first for risk assessment.<sup>1</sup> Such patients are at higher risk than the general population, and the 'number needed to screen' to find an individual with more than a 30% 10-year risk is therefore reduced through this strategy. However, those at highest risk tend to be the older patients in all risk factor groups, and the effect of age may outweigh the other major factors. In the age group 35–39 years, the number needed to screen is greater than 1,000 for both men and women, but only 10 for men and 75 for women aged between 60 and 64 years.<sup>15</sup> Eighty-five per cent of the population's avoidable cardiovascular disease is to be found in the 16% who are over 65 years old.<sup>16</sup> Clinical intuition is not a sufficient means of reducing the number needed to screen, and subjective estimates of individual risk by general practitioners or practice nurses are inferior to computer-assisted risk calculations.<sup>17</sup>

### A new targeting strategy

Candidates for primary prevention screening could be identified electronically by roughly estimating the 10-year risk on all patients in the practice, based on the most recent values of the existing coded risk variables, or, in the case of systolic blood pressure, an average of the last two measurements — this is the mechanism used by the current EMIS system to calculate the risk of individual patients. Those patients on treatment for hypertension or hyperlipidaemia would need to be identified with a lower threshold, because they will have a higher risk when assessed using pretreatment levels. Existing computer software in primary care can make such a distinction electronically. While the Framingham algorithm is designed to predict outcomes using pretreatment blood pressure and lipid levels, the same algorithm might be used as a starting point for assessing modified risk and then adjusted according to outcomes using the adaptive prediction model. This would provide essential information on the impact of treatment on risk which is not available from the Framingham study.

In this way, the computer could, through regular searches, identify patients who were actually or potentially drifting into the greater-than-30% range. The practice could then be informed, perhaps on a 3-monthly basis, of all such patients, who would be identified anonymously using electronic record numbers and listed in order of suspected risk. The interval could be adjusted according to available time and resources.

So far, this process could all be carried out at practice level without the need for extraction of data by an external agency, but the pooling of data nationally would have one further potential benefit: adaptive learning of the prediction algorithm. The healthcare system in the UK, as opposed to the United States, is equipped to quickly build predictive models from data collected in the process of care, including models that take into account regional differences in terms of patient population and practice variation.

### Adaptive learning

Linking practices by pooling extracted data would, in principle, enable the adaptive prediction model to adjust its internal parameters in response to observed outcomes (namely, the development of coronary heart disease and stroke). This 'reprogramming' is possible because the same database that provides the values of the Framingham variables also contains the dates when each patient who later developed coronary heart disease was diagnosed. The ability of existing computer software to examine data retrospectively on the timing of coronary heart disease onset has already been demonstrated.<sup>18</sup> In principle, therefore, all the information needed to retrain the model is present within the system (Figure 1).

An example of where such modification might occur concerns the predictive values of systolic and diastolic blood pressures, and pulse pressure in relation to age. There is recently published evidence from the Framingham study that diastolic blood pressure is a more reliable predictor of future cardiovascular outcomes in younger patients compared with older ones, in whom systolic pressure is more reliable.<sup>19</sup> Above a certain age, pulse pressure may then become the best predictor. An adaptive predictive model would eventually produce the best prediction it could for each age group when exposed to enough data over extended time periods, recognising that the weights appropriate for the systolic and diastolic blood pressure values would be partly dependent on the value of the age variable.

### Advantages of an adaptive prediction tool built with primary care data

The targeting of individuals for risk assessment would be improved by using expected overall risk as the basis for patient selection, rather than a diagnosis of diabetes or hypertension. The electronic retrieval of any of the other variables, the most important of which is age, would assist in reducing the number needed to screen.

Patients who are not diagnosed with hypertension but who have raised blood pressure measurements, and who represent a significant case volume,<sup>20</sup> would be included in the screening process because they would be identified by their blood pressure values, and not on the basis of inclusion in the hypertension disease register.

Where data are missing, a different predictive model could be used (although data should become increasingly complete over time within the higher risk groups).

By measuring risk using the most recent input variable values, the model can monitor the adequacy of risk modification in a practice population, making it amenable to audit. Decisions about treatment can still be based on pretreatment blood pressure and lipid levels, as recommended in the NSF.

The cyclical nature of the process, like the traditional audit cycle, means that improvements are progressive, and patients moving into the high-risk category over time can be recognised. High-risk patients are a dynamic subgroup that is constantly revising its membership. This dynamism needs to be reflected through a targeting policy that is ongoing rather than a 'once-only' exercise.

Those patients at high risk, whose blood pressure defies reduction to target levels through drug treatment can, nevertheless, have their overall risk reduced by the use of combined approaches. This process is facilitated through the monitoring of modified rather than pretreatment risk.

### Discussion

The targeting phase of this model has no minimum quality requirement other than an electronic age and sex register, but the adjustment of the algorithm would only be appropriate if data quality were maintained at a high level, creating numerous difficulties. In particular, the measurement of blood pressure would need to be carried out by adequately trained staff, in line with recommended practice.<sup>21</sup> Blood pressure measurements taken by primary care clinicians in busy surgeries, and on patients who may be unwell at the time, may differ from those gathered in the less pressured conditions of a prospective cohort study. Coded outcome measures would need to include all cardiovascular events, including sudden cardiovascular deaths, while morbidity registers for coronary heart disease in general practice are currently of variable quality.<sup>22</sup> Recorded dates of the onset of cardiovascular disease may be delayed following presentation while investigations are undertaken to confirm the diagnosis. Other influences might also undermine the model's validity; for example, financial incentives based on achievement of blood pressure targets rather than on the quality of data recording. Patients moving from one practice to another would need to be identifiable in order to match predictions with outcomes, and might be lost in the process. This problem of 'data censoring'<sup>23</sup> can be accounted for in some of the statistical models proposed above, in order that the information is still useful even if incomplete, but it will remain an issue.

It is therefore likely that some of the participating practices across the UK, with a commitment to maintaining high-quality data and accurate, up-to-date disease registers for both coronary heart disease and diabetes, would need to be identified (Box 3) in order to minimise these obstacles. It might be hoped that the usefulness of the tool would motivate participants to enter high-quality data. The sheer quantity of information available, which would soon exceed any past cohort study, might address questions previously unanswerable owing to inadequate sample sizes. Other

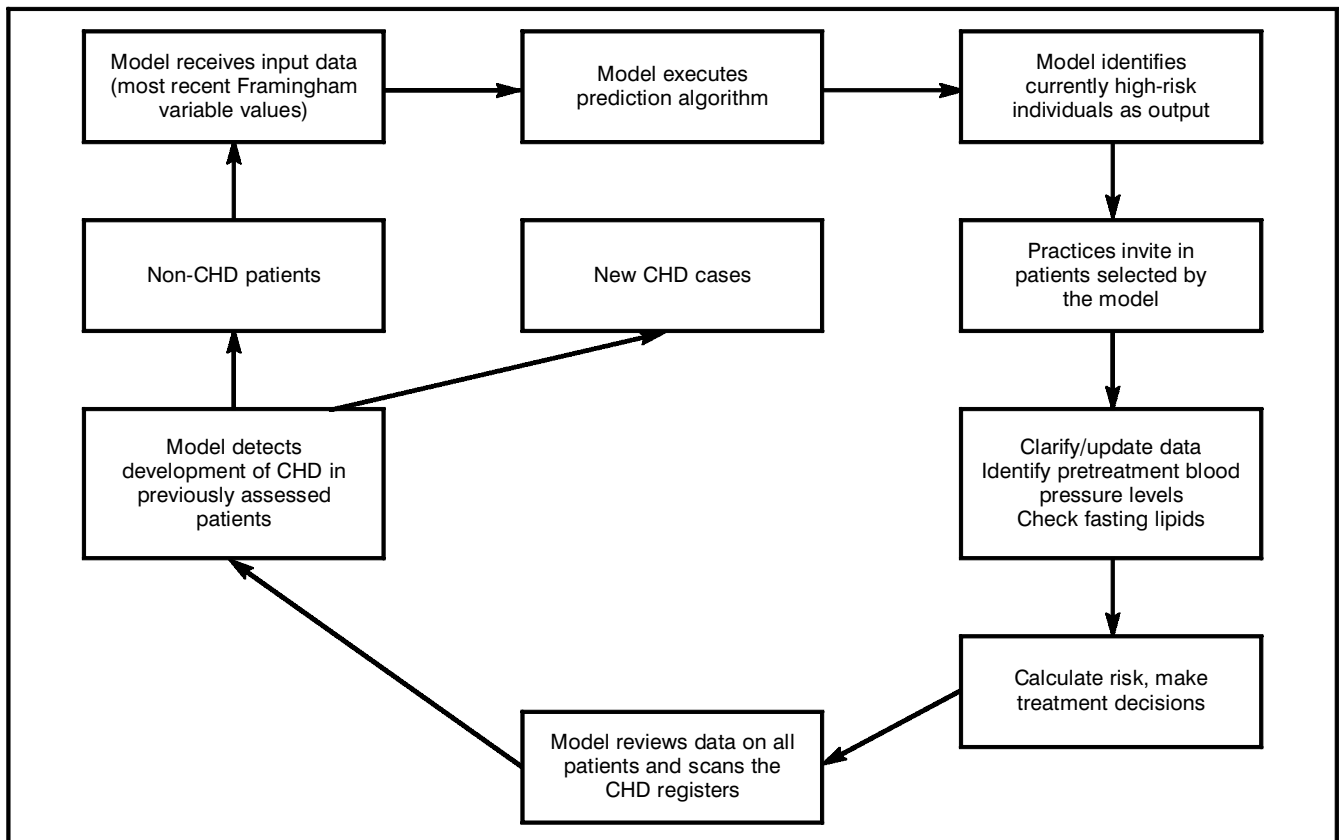


Figure 1. A nationwide adaptive prediction model for coronary heart disease (CHD) prevention. The development of new CHD cases in the population is detected by scanning the CHD register during each cycle. These outcomes are then allowed to modify the prediction algorithm, if necessary, by comparing past risk factor patterns with outcomes in both CHD and non-CHD cases.

- Routine electronic recording of all the Framingham input variables
- Separate electronic disease registers for type 1 and type 2 diabetes
- A coronary heart disease register with accurate dates of onset
- Blood pressure measurements carried out by adequately trained personnel
- A policy of testing for diabetes in patients undergoing cholesterol estimation
- Electronic recording of anti-hypertensive and lipid-lowering medication use
- Coded recording of deaths from cardiovascular disease

Box 3. Minimum data quality standards for participating practices.

factors known to influence risk could be included, and the minor variables might become more important when present in certain combinations, as seen in the example from Baxt discussed above.<sup>8</sup> Such combinations might occur rarely, even in a large cohort study population, and their predictive value may therefore escape recognition. In principle, the model could use any relevant factor that is recordable electronically, including the use of drugs such as aspirin, angiotensin-converting enzyme (ACE) inhibitors, and beta-blockers, as well as the known missing factors discussed above.

The adaptive prediction model would need to be poised to respond to changing patterns with an appropriate sensitivity, in order that only statistically significant trends are allowed to lead to modification of the algorithm. It might be expected that an adjustment in the algorithm would occur initially as a result of risk differences between the original Framingham cohort and the current UK population. Thereafter, more gradual changes might be seen as an adaptation to demographic and genetic changes in the UK population.

The model could only be as 'smart' as the data allowed, and unless given information on ethnicity (which is not routinely recorded electronically), it could not allow for the known differences in risk between different ethnic groups. In practice, however, human involvement, which is of course invaluable to the process of communicating risk and advising on lifestyle modification and treatment to individual patients, would still, under this proposed strategy, allow this and other missing factors to be taken into account when planning treatment, as recommended under the current policy. Coronary heart disease prevention is a challenging area of primary care. This model can only assist in certain stages of a complex process, but might enable resources to be targeted more effectively, advice to become more sensitively tailored to the individual, and in the process generate information for research through a novel mechanism involving practising clinicians in the natural environment of everyday care.

Coronary heart disease prevention is an obvious example where a framework for standardised electronic recording has been specified in the NSF, and a prediction algorithm is already in widespread use. Other potential applications include the assessment of predictive values for primary care symptom complexes<sup>24</sup> and the prognosis of malignant disease in individual patients.<sup>25</sup>

## Conclusion

The development of computerised disease registers and the electronic recording of values for cardiovascular risk factor variables open up the possibility of a nationwide adaptive prediction tool, which would be capable of pooling data from a large number of participating practices committed to high-quality data recording. Such a model would function as a pattern recognition device, identifying candidates for coronary heart disease risk assessment and allowing risk control to be monitored at the population level.

In principle, the model could improve the accuracy of predictions currently made through the Framingham algorithm over time, by responding to significant trends in the patterns of coronary heart disease risk in the UK as they develop during the 21st century. Where data quality allows, the same method could be applied to other areas of clinical care, and may help to bridge the gap between research and practice. This provides a further stimulus for the integration and standardisation of electronic record keeping in primary care.

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students in public and private schools was 18.3% and 8.1%, respectively—perhaps because of improved information dissemination and greater stress on health education in private schools compared with public schools. In all, 62% of adolescents reported their reason for smoking as enjoyment, while 18% claimed to have been influenced by advertisements to begin smoking. The majority of students (61.3%) were smoking with their friends. In this study adolescents also reported family tobacco use: father 19.8%, mother 27.8%, brother 21.0%, and uncle 27.1%. Multiple logistic regression analysis of factors associated with smoking revealed that after adjustment for age, ethnicity, and place of residence, students in public schools were more likely to be smokers compared with those in private schools (adjusted odds ratio [OR] = 1.6; 95% CI: 1.0, 2.7). Adolescents were more likely to be smokers if their peers were smokers (adjusted OR = 6.2; 95% CI: 3.91, 9.9). Boys who spent most of their leisure time outside their homes were more prone to smoke cigarettes (adjusted OR = 3.9; 95% CI: 1.2, 13.2) as were those who had a smoker in the family (adjusted OR = 1.7; 95% CI: 1.1, 2.8). During adolescence, tobacco use by peers may create a positive image of smoking and create easy access to cigarettes, especially in developing countries where there are no restrictive laws on the sale of cigarette to minors. The findings presented in this study

are consistent with other studies conducted on adolescent smoking behaviour, which showed that parents, siblings, and peers are powerful influences for adolescent smoking.<sup>5</sup> Smoking is usually initiated during adolescence and being amenable to behaviour modification it should become a public health priority to educate adolescents and parents regarding hazards of smoking in Pakistan and other developing countries.

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## Cardiovascular risk assessment—time to look beyond cohort studies

From PETER M BRINDLE<sup>1</sup> and TIM A HOLT<sup>2</sup>

Sirs—In the April issue of the *International Journal of Epidemiology*, Hans-Werner Hense provides a comprehensive treatise on the current state of cardiovascular risk assessments.<sup>1</sup> He highlights the problems with using risk scores derived from epidemiological data to target preventive treatment at highest risk individuals. His comments add to the growing literature recognizing that the risk assessment methods used in current treatment guidelines do not provide an accurate assessment of an individual's true risk.<sup>2,3</sup> Hense identifies some of these potential sources of inaccuracy: the variation of cardiovascular risk between populations, using predictions based on assessment of risk factors at one occasion only, the confusing variety of endpoints used in different risk scoring methods, and the 'contamination' of risk predictions by risk-reducing treatments such as blood pressure lowering drugs. Hense also highlights the important, but often unrecognized, implications of basing treatment on different thresholds of risk. For example, when the threshold is  $\geq 30\%$  10-year risk of coronary heart disease, around 84% of the disease events may occur in the 'low risk' group—people who might potentially be reassured by the decision that treatment was not indicated for their level of risk. When the threshold is  $\geq 15\%$ , this false negative rate falls to 25%, but the number identified as being at high risk yet do not

have a cardiac event rises from 6% to 45%.<sup>2</sup> Hense is right to say that this information is implicit in the particular thresholds that are chosen, but unfortunately guideline authors or practising clinicians are rarely so explicit. Clinicians might wrongly assume that population screening to identify high risk individuals is supported by evidence of effectiveness and meets the basic requirements of a screening test.<sup>4</sup>

As well as listing the problems with cardiovascular risk assessment, Hense offers some solutions. These include the re-calibration of risk functions to regional event rates, and the pooling of cohort studies to limit the influence of regression dilution bias. He identifies the approach adopted by the SCORE (Systemic Coronary Risk Evaluation) investigators of pooling data from 12 European cohorts, and providing risk assessment charts for high and low risk countries.<sup>5</sup> Unfortunately, the SCORE approach is limited by the use of cardiovascular death as its endpoint and it does not have an indicator variable taking into account treatment effects. The SCORE project represents an impressive collaboration that will have entailed a considerable amount of work to obtain, clean, and pool such a diverse collection of datasets. However, it is not certain that the advantages over the available Framingham scores are sufficient to have justified such effort. A simpler approach might have been to use the published Framingham score that adjusts for hypertension treatment effects, and re-calibrate it for different regions within Europe using a method previously described.<sup>6,7</sup> Additionally, the SCORE algorithm in its current form cannot be used in many inner city family practices where the majority of the patients live in areas of

<sup>1</sup> Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol BS8 2PR, UK.

<sup>2</sup> Department of Primary Health Care Studies, University of Warwick, Coventry CV4 7AL, UK.

socio-economic deprivation or are from black and minority ethnic groups. Consequently, the SCORE approach only represents a minor tweaking of the 'one size fits all' approach.

To improve the discrimination of risk scores, we need a better understanding of the cardiovascular disease process and Hense suggests including new biochemical and other variables to identify sub-clinical disease. Although the predictive accuracy may be improved, the inclusion of additional variables requiring specialized equipment will cause the acceptability and clinical application of the risk assessment tool to suffer. Collection of basic risk factor information such as high-density lipoprotein cholesterol by primary care teams is at best inconsistent, so inclusion of these 'new' risk factors in a clinically valid risk score may not improve population screening in the short or medium term.<sup>8</sup>

It is unlikely that risk scores derived from cohort studies designed primarily to investigate aetiological rather than prognostic factors related to cardiovascular disease will ever be sufficiently flexible to fully take into account the issues of generalizability, measurement error, treatment effects, and temporal changes in disease incidence. Increasingly large volumes of data related to cardiovascular disease are now routinely collected in standardized form from primary care as a way of monitoring the performance and quality of primary care practitioners. Information technology systems are now sufficiently sophisticated for data held at the practice level to be remotely accessed and analysed by a central system. Risk factor and outcome information collected on millions of individuals will provide an extremely powerful resource for developing risk prediction models. If details of ethnicity were collected, this would remove the problem of a shortage of relevant incidence data within European countries. New, adaptable statistical approaches are required, such as neural networks that are able to modify their predictions or 'learn' from new risk factor and outcome information from these routine data sources.<sup>9</sup>

There is no doubt that using a multi-factorial score to guide the clinician in targeting preventive treatment is preferable to managing patients on the basis of arbitrary levels of single risk factors. The use of various risk scoring methods can play an important part in educating the clinician and the patient about the contribution that lifestyle and physiological measures make to overall risk, and also help with understanding the benefits of preventive intervention. However, the development of more accurate and practical risk scoring methods that are relevant to primary care teams has stalled. A single risk assessment method, such as the Framingham coronary risk score, that is not tailored to the individual situation of the patient, does not provide patients and their doctors with sufficiently accurate information

to make major treatment decisions. The pooling of many similar cohort studies to derive a score adapted to national levels of cardiovascular disease offers only a limited advance. Much greater imagination is required to make the most of the huge volumes of regularly updated information on cardiovascular disease that is routinely collected in primary care. The data could be used to devise locally adaptable risk assessment methods that automatically calculate an individual's risk from the available data. Doctors and nurses perform risk assessments with only moderate accuracy,<sup>7</sup> so this automation would take the process of performing the risk assessment from the time-limited doctor's consultation and allow the creation of a register of high risk patients. The seamless integration with the consultation, of a continually updated risk score derived from patients in primary care, would overcome the major deficiency of even the most accurate risk scoring tool—that is of being used incorrectly or not being used at all.

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## Case studies

# The South Warwickshire NHS Care Records Service Demonstrator Project: lessons for the National Programme for IT

Ian Allwood MB BS DCH DRCOG

South Warwickshire PCT Professional Executive Committee Modernisation Lead and General Practitioner, Stratford upon Avon, UK

Tim A Holt MB BS DRCOG MRCP FRCGP

Clinical Lecturer, Centre for Primary Healthcare Studies, University of Warwick and General Practitioner, Kenilworth, Warwickshire, UK

### ABSTRACT

The NHS Care Records Service (CRS) is a major goal of the National Health Service (NHS) Modernisation Programme. It will provide for 24-hour access by clinicians to electronic patient records and the integration of information from previously separate databases, reducing the 'seams' between primary and secondary care, between out-of-hours and ordinary working hours, and ultimately between health and social care. Such integration is likely to affect not only individual patient care, but also public health including disease surveillance, and the monitoring of clinical activities including the achievement of clinical governance targets. The potential benefits for patients, practitioners and managers are numerous. However, the process raises issues over confidentiality, data protection and data

quality. During 2003 a project was undertaken in South Warwickshire to develop an NHS CRS widely available to primary care clinicians in the region. This was part of a wider initiative funded by the NHS Connecting for Health (NHS CfH). Twenty-six out of 36 local practices took part, providing a combined database of 181 961 clinical records. All but one of the original objectives was achieved. Lessons were learned which could usefully inform the development of the CRS more generally in the NHS.

**Keywords:** care records service, information storage and retrieval, medical records systems – computerised, interoperability

## Introduction

A number of recent directives point towards database integration as the way forward for health informatics in the National Health Service (NHS), including *Information for Health* and *Delivering 21st Century IT Support for the NHS: national strategic programme*.<sup>1,2</sup> Significant barriers remain, however, particularly at the interface between health and social care.<sup>3</sup> These include not only issues of confidentiality and patient consent, in the context of the 1997 Caldicott Review and the 1998 Data Protection Act, but also those of data quality and software compatibility.<sup>4-6</sup> Potential benefits of database integration include access to clinical records, investigation results, and allergy and medication histories by clinicians dealing with patients 'out of hours';

electronic linkage between primary and secondary care units; the detection of population-level changes in morbidity patterns, including infectious diseases; improved communication between professionals using the databases; and, increasingly, the use of such data for research.

Twenty-four-hour emergency access to medical records is one of the defined objectives of *Information for Health*, to be achieved by 2005. Because these records are traditionally held in general practice (GP) premises, and such premises are no longer the usual point of delivery of out-of-hours care, this objective unavoidably requires external access to practice-held records. The move towards increased access and

information flow may be contrasted with the 'need to know' principle that is central to the Caldicott Review.<sup>4</sup> For an integrated database system to satisfy both guidelines, clearly defined protocols governing rights of access are required. One of the successes of the project we describe was the achievement of this outcome. The project objectives are shown in Box 1.

### Box 1 Project objectives

- To create a working model of rapid primary care record integration for South Warwickshire Primary Care Trust.
- Where applications cannot be demonstrated within the schedule, to complete the design and planning to illustrate what can be done and how.
- To explore the implications and benefits in process and technical terms of using the Demonstrator and of hosting GP software systems.

## The South Warwickshire Demonstrator Project

South Warwickshire Primary Care Trust (PCT) is situated in the West Midlands, south of Coventry and Birmingham, serving a population of 249 000. A district general hospital at Warwick provides the majority of secondary care services. Within primary care there are 36 general practices and approximately 142 general practitioners. At the time of this project all the practices were computerised to varying degrees and the majority had links to hospital databases for transmission of laboratory data. In addition to general practices, GP hospital facilities, physiotherapy units and NHS Acute Trust community clinics took part in this project.

The global information technology (IT) company IBM and Newchurch (a United Kingdom [UK]-based private health informatics company that specialises in primary care database management) were contracted to manage the project in collaboration with local stakeholders.<sup>7</sup> Newchurch were responsible for the protection of data held in a central repository located at Teddington, Greater London. Every 24 hours the repository was updated by downloads from the source systems. Data quality was improved by cleansing and standardising the coding. This information was accessible to authorised users over the NHSnet, and access to the repository occurred both through fixed-line NHS connections and mobile devices. The user interface, the 'Primary Care Information Solution' (PCIS), was available at 320 access points at general practice surgeries, hospital Accident & Emergency (A&E) departments, GP hospital wards and community-based

clinics. Each user accessing the system was allocated a security level. 'Sensitive' or 'confidential' information was identified and the user's security level determined how much information was accessible to that user. Whilst the project was established on the basis of 'implied consent' (patients aware of the project through publicity and unhappy about it could withhold their records, but otherwise would be included), access only *actually* occurred with the patients' *expressed* consent at the point of care. For instance, a patient seen in the A&E department would be asked to consent to access to their general practice records by A&E staff. This process could be overridden if the patient was too unwell to discuss it, but otherwise ensured that a patient unaware of the project could dissent to access if they wished. Staff undergoing training in the use of the system were made aware of the audit trail facility which records every instance of access, including the user's identifier.

### Software compatibility

In addition to confidentiality issues, a further obstacle to database integration is the diversity of software providers in primary and secondary care. To overcome this problem, a wider system capable of incorporating a number of software providers was required. The Health Care Interoperability Forum (HCIF) exists to promote information flow and the operability of alternative software in the shared NHS environment.<sup>8</sup> The HCIF is a UK-based commercial co-operative that subscribes to Health Level 7 (HL7), an international body 'providing standards for the exchange, management and integration of data that support clinical patient care and the management, delivery and evaluation of healthcare services'.<sup>9</sup> The UK component, HL7UK, provides the currently accepted guidance on interoperability within the NHS. The software systems involved included: from general practice: EMIS, Vision and Torex (now iSOFT) GP systems; from the PCT: CISS (Community Services) and CPA (Mental Health) Systems; and from Warwick Hospital: Torex PAS and Anglia Reporting Systems. Data flow between different web-based units was facilitated through the use of extensible mark-up language (XML). XML is a more flexible language than hyper text mark-up language (HTML) but is simpler to program and more usable than standard generalised mark-up language (SGML). The use of XML in this project was an important means of achieving interoperability.<sup>10</sup>

This project, funded by the NHS Programme for IT, was one of a number of similar initiatives, including Electronic Record Development and Implementation Programmes (ERDIPs).<sup>11,12</sup> The collation of information on the same individual from different sources was made possible by the use of a Master Patient Index (MPI).

## The Master Patient Index

The MPI is based on patients' NHS numbers, allowing 'registration' to occur above the practice level. The current system of practice-based registration (in which patients registering with a new practice automatically trigger the cancellation of their previous registration) ensures that they can no longer be registered in more than one general practice. This contrasts with other medical registers (such as hospital laboratory databases) where it is not as easy to ensure that the same patient won't be counted twice. The same MPI principle has been used in Canada, where the Integrated Health Research Network database collates information across Quebec, serving an integrated system of care between hospital and community services.<sup>13</sup> In the MPI used in this project, NHS numbers were aligned with PCT-held patient demographics and Warwick Hospital casenote ('UR') numbers, in order that both hospital and community data could be integrated without duplication. The prime identifier for all patients was their NHS number.

## Outcomes of the project

### Box 2 Outcomes of the CRS Demonstrator Project

- 26 out of 36 practices daily contributed data to a centrally hosted CRS repository. This represents approximately 181 961 patients from a total list of 249 000, or 73% of the PCT's active patient list
- 498 user identifiers issued and 300 staff attended formal PCIS training sessions
- Integration with CISS (Community Health), CPA (Mental Health), Pathology and Radiology, providing a wide range of patient data available to authorised users
- The creation of a security model, accommodating PCT and practice positions on confidentiality and consent within available national guidance
- Agreed security profiles for different categories of users of the central system (GPs, practice staff, out of hours, A&E, mental health professionals, non-mental health clinicians)
- System configured to meet the needs of primary health community and participating acute trust groups
- The ability to view radiology and pathology results associated with the patient record

Box 2 lists the main outcomes following completion of the project in September 2003, and Box 3 shows more recent data on usage of the system. The majority (26/36: 72%) of general practices in the area were willing to take part. A small number (2/36: 5%) were unhappy about the confidentiality issues, whilst eight practices did not respond to the invitation to participate. This represents approximately 181 961 patients from a possible total of 249 000, or 73% of the PCT's active patient list. The participating practices, as well as other healthcare facilities in the area, hosted a total of 320 instances of Newchurch's PCIS, a standard user interface. Three hundred NHS staff attended training sessions, and a total of 498 user identifiers (at varying levels of access) were issued. This led to an integration of a wide range of information sources across primary and secondary health care, and mental health. The most recent Department of Health guideline, *Confidentiality: NHS Code of Practice* was not published until the end of July 2003, but this project was operated in accordance with guidelines available at the time and was compatible with this document.<sup>14</sup> The total cost of the project was £1 477 417, falling within the £1.5 million budget available. The software was originally designed to update the central repository every 30 minutes, but for the duration of the project it was not possible to improve on the 24-hour cycle achieved. It is hoped that the cycle might be shortened through further work in the future in order to move the operation closer to 'real time'.

### Box 3 Usage of the system

- There are 320 instances of the PCIS at general practices, community health offices, GP wards, physiotherapy, the A&E department of Warwick Hospital, and other centres.
- Between January and July 2005, there were approximately 7200 log-ins to PCIS from practices, non-practice users and the PCT. Approximately 25% of activity arises from A&E departments in the region.

## Lessons learned

The following issues arose during this project, and are discussed in more detail in the End Project Report:<sup>15</sup>

- 1 *A CRS based on GP records is possible to implement and can lead to improved patient care.* The project was delivered within the anticipated time-scale and the overall budget. Examples of comments from system users are given in Box 4.
- 2 *IT needs integration with change management for rapid adoption.* The project suffered from a lack of

incentives beyond the perceived utility of the end result, and receptiveness was variable. Participation was voluntary, and as the facility was not underpinned by a specific change management programme, the CRS was seen by some as an IT initiative rather than a wider modernisation opportunity. Most activities in the project required negotiation with clinicians for access to services, and this inevitably took a lower priority to clinical care.

- 3 *Confidentiality and consent issues.* Lacking precedents on which to base specific confidentiality guidelines, the model was developed through extensive discussions between the project board, patient representatives, PCT Caldicott Guardians and practices. This process took longer than expected, but was felt to be crucial to the project. The need for detailed negotiation must be accounted for in planning and scheduling similar projects elsewhere. A nationally agreed ethical framework for such projects would assist considerably, but there will always be local issues and obstacles to negotiate.
- 4 *New communications strategies are needed.* Apart from the PCT board, a number of local stakeholder groups received formal presentations, including the Acute Trust Board, the Medical, Nursing and Allied Health Professionals Committees, the Shadow Patient Council and the Community Health Council. Progress on the project and its outcomes were also communicated through PCT newsletters, and through direct communications from the GP 'champion' and the PCT IM&T manager to local practitioners and users. However, a future communication strategy could be more tailored to the needs of disparate users from different backgrounds, to avoid the information overload that can easily result in the 'default delete' option when presented with promotional material.
- 5 *An integrated environment introduces complexity.* The project identified the need for a Representative User Forum to advise on the delivery of the project and prioritise any enhancements. Such a forum was initially involved in the early stages but tended later to fragment so that advice was gained from individuals rather than the forum itself thereafter. There were problems integrating certain hospital casenote ('UR') numbers with NHS numbers, and the more widespread use of NHS numbers would have simplified integration. The system was operated through the NHSnet and was therefore dependent on its performance. During August 2003 the MSBlast virus, which caused extensive damage to web-based systems generally, resulted in a failure of retrieval of data to the central repository for eight days, requiring a catch-up period. Future developments of the CRS will require attention to this issue of vulnerability at the system level.

6 *Don't call it a 'Demonstrator'.* This term tended to portray an experimental rather than ongoing status for the project, which meant that some individuals were unclear how much it justified their time. Extension of funding has enabled the system to remain in operation following the end of the project.

7 *Strategic health authorities, PCTs, GPs and suppliers can work together to achieve a CRS.* The project benefited from excellent relationships between all the parties concerned, who shared common aims and objectives. The CRS both requires and builds on such relationships through its integrated structure.

#### Box 4 Examples of user feedback

'With the PCIS we were able to obtain information on the drugs that the patient took regularly, giving us the knowledge of what a patient's drug history was.'

'An elderly lady came to A&E in an ambulance from a nursing home without a nurse in attendance. When the doctor started to take the history, it was evident that she was unable to recall her past medical history. PCIS enabled us to get this, which then enabled us to deliver appropriate nursing care.'

'The patient had an ECG taken which showed an arrhythmia; we needed to establish whether this was new or old. By accessing the PCIS we were informed that it was old and therefore prevented a hospital admission.'

'The PCIS enables us to establish what a patient's tetanus status is.'

'The patient said that the morning pills she took were white, and the evening pills were pink; PCIS provided us with the information to establish the names of the drugs she was taking.'

## Discussion: the future

The technical success of this project in providing a shared software environment for the NHS Care Records Service at the PCT level was clearly demonstrated. In the process, a number of issues relevant to the ongoing national integration of NHS databases were identified.

Obstacles to integration include technical issues such as software compatibility and standardisation of record keeping.<sup>16</sup> Huston emphasises that information technology itself will not solve the problem of

poor record keeping, and recommends that clinicians rather than managers should lead the process of standard setting.<sup>17</sup> Data quality is also a potential problem. Ideally, universal patient identifiers are required for optimal record linkage, and inaccuracies in patient records might in theory be amplified by database integration.<sup>18,19</sup> Methods of measuring data quality are known, but patients may remain concerned unless ownership of information is clear and strictly controlled, so that the benefits of information sharing can occur without loss of confidentiality.<sup>20,21</sup> In a qualitative practice-based study, Ward and Innes have shown that whilst patients expect their doctors to limit access to their records appropriately, they also expect them to make relevant information quickly available across the health service where needed.<sup>22</sup> This is a difficult but important balance to strike.

This project was undertaken within a fixed time-scale and budget, but the facility remains in use and could be extended in future as the NHS undergoes further modernisation. Access to the system from secondary care (other than GP wards) was limited to A&E, but PCIS units could in principle be set up in hospital outpatient departments as well as inpatient wards, intensive care units or theatre recovery. The system may also be used to support the development of GPs with Special Interests (GPSIs), as this role expands in future years. The Master Patient Index, which allows PCT-level registration to occur, could be used to provide more adequate registers for specific clinical conditions. These not only include diagnostic groups (such as diabetes, for the targeting of patients for interventions such as community retinal photography), but also those with different conditions but sharing similar or overlapping needs. An example of this is the 'ELDIT' study (Epidemiology of Liver Disease In Tayside), which used the same principle of database integration, including biochemistry, immunology and virology laboratory sources.<sup>23</sup> Diagnostic algorithms have been applied to this combined database to classify individual cases, recognising patterns through collation of information from multiple sources. In addition to established conditions, data from previously isolated sources might facilitate the identification of patients *at risk* of certain conditions, where risk factor profiles are complex. These might include children at risk of abuse, or the identification of patients likely to require hospital admission in the near future, an area currently under investigation by the King's Fund.<sup>24</sup> The latter two groups might particularly benefit from the inclusion of social services data, not included in this South Warwickshire project but a potentially valuable source for inclusion in the future. Similarly, the inclusion of dentists' and opticians' reports might further amplify the potential of the model for inter-professional communication to the benefit of patients.

## Limitations and future research needs

This case study has described the establishment of a local Care Record Service in South Warwickshire. The benefits of this service have not yet been formally researched following the project's completion, but during its creation the same sorts of issues and obstacles to implementation found elsewhere were identified.<sup>25</sup> To justify the costs of such systems, added value above existing facilities to both patients and clinicians need to be demonstrated.<sup>26</sup> In a series of case studies and in-depth interviews across four acute NHS trusts, Hendy *et al* have uncovered the 'sociocultural' as well as logistic challenges of such integration, particularly within the time-scales initially proposed by NHS Connecting for Health.<sup>27</sup> This Demonstrator Project needs to be similarly researched through a more extensive evaluation of the system's usage, exploring not only the technical and logistic barriers to its ongoing delivery, but also the qualitative issues of acceptability and perceived benefit from the perspectives of patients and practitioners.

### ACKNOWLEDGEMENTS

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#### CONFLICTS OF INTEREST

None.

#### ADDRESS FOR CORRESPONDENCE

Dr Tim A Holt  
Clinical Lecturer  
Centre for Primary Healthcare Studies  
University of Warwick  
Coventry CV4 7AL  
UK  
Tel: +44 (0)2476 574898  
Email: [tim.holt@warwick.ac.uk](mailto:tim.holt@warwick.ac.uk)

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Study protocol

Open Access

# Protocol for the 'e-Nudge trial': a randomised controlled trial of electronic feedback to reduce the cardiovascular risk of individuals in general practice [ISRCTN64828380]

Tim A Holt\*<sup>1</sup>, Margaret Thorogood<sup>1</sup>, Frances Griffiths<sup>1</sup> and Stephen Munday<sup>2</sup>

Address: <sup>1</sup>Health Services Research Institute, Warwick Medical School, Gibbet Hill Rd, Coventry CV4 7AL, UK and <sup>2</sup>South Warwickshire Primary Care Trust, Westgate House, Market St, Warwick CV34 4DE, UK

Email: Tim A Holt\* - [tim.holt@warwick.ac.uk](mailto:tim.holt@warwick.ac.uk); Margaret Thorogood - [margaret.thorogood@warwick.ac.uk](mailto:margaret.thorogood@warwick.ac.uk); Frances Griffiths - [f.e.griffiths@warwick.ac.uk](mailto:f.e.griffiths@warwick.ac.uk); Stephen Munday - [stephen.munday@SwarkPCT.nhs.uk](mailto:stephen.munday@SwarkPCT.nhs.uk)

\* Corresponding author

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## Abstract

**Background:** Cardiovascular disease (including coronary heart disease and stroke) is a major cause of death and disability in the United Kingdom, and is to a large extent preventable, by lifestyle modification and drug therapy. The recent standardisation of electronic codes for cardiovascular risk variables through the United Kingdom's new General Practice contract provides an opportunity for the application of risk algorithms to identify high risk individuals. This randomised controlled trial will test the benefits of an automated system of alert messages and practice searches to identify those at highest risk of cardiovascular disease in primary care databases.

**Design:** Patients over 50 years old in practice databases will be randomised to the intervention group that will receive the alert messages and searches, and a control group who will continue to receive usual care. In addition to those at high estimated risk, potentially high risk patients will be identified who have insufficient data to allow a risk estimate to be made. Further groups identified will be those with possible undiagnosed diabetes, based either on elevated past recorded blood glucose measurements, or an absence of recent blood glucose measurement in those with established cardiovascular disease.

**Outcome measures:** The intervention will be applied for two years, and outcome data will be collected for a further year. The primary outcome measure will be the annual rate of cardiovascular events in the intervention and control arms of the study. Secondary measures include the proportion of patients at high estimated cardiovascular risk, the proportion of patients with missing data for a risk estimate, and the proportion with undefined diabetes status at the end of the trial.

## Background

### Primary research question

Can an automated system of electronic feedback (e-Nudge) reduce the incidence of cardiovascular events in high risk patients in general practice, compared to "usual care"?

## Background

A major focus of chronic disease management is the prevention of cardiovascular disease (CVD). An important development occurred in UK primary care in April 2004, with the introduction of the "new General Medical Services Contract" (nGMS) [1]. This involved the establishment of registers for a number of conditions relevant to

CVD prevention, and the resulting standardisation of electronic record keeping has made the data potentially useful for research [2]. The Quality and Outcomes Framework (QOF) of the nGMS specifies targets for blood pressure, serum cholesterol levels, and smoking cessation advice for patients with hypertension, diabetes, or established CVD. Whilst not included in the QOF, the Coronary Heart Disease (CHD) National Service Framework (NSF) [3] also recommends the systematic identification of patients at high risk of CHD but who are not yet displaying any symptoms.

For many patients, the need for preventive treatment is clear, for example through a diagnosis of CVD or diabetes, but for others, the overall cardiovascular risk should be taken into account when determining the need for treatment of hypertension or hypercholesterolaemia. This strategy is strongly supported by the recently published Joint British Societies guidelines on prevention of CVD in clinical practice [4]. This project will assess the effectiveness of targeting patients who are the most likely to benefit from risk factor modification on the basis of their absolute risk of cardiovascular events.

#### **Changing clinical behaviour through electronic reminders**

Despite increasing use of electronic reminders and alert messages, there are relatively few controlled trials that demonstrate their ability to modify clinical behaviour, and none so far carried out in the UK under the new General Practice contract. Published literature is largely concerned with the following uses of these tools:

- to increase physician or nurse adherence to guidelines on best practice in the clinical environment [5], including the use of drug therapy [6]
- to increase the uptake of vaccinations [7-11]
- to promote other preventive health care activities, by triggering opportunistic interventions including screening [12], monitoring [13,14], diagnostic tests [15], and lifestyle counselling [16,17]
- to increase the cost-effectiveness of health care, by avoiding duplication, facilitating communication between members of the health care team [18], and reducing the need for recall of patients through increased use of opportunistic activities during consultations

Of these, the most successful area is vaccination uptake, where a number of studies have demonstrated benefit [7-10], and in the avoidance of prescribing errors, where alerts have been shown to be effective in decreasing the ordering and administration of contraindicated drugs, for instance due to renal insufficiency [19].

Results in other areas have been mixed [20], and may depend on the response of the clinician to the alert message, which must therefore be appropriately designed [21]. In a United States outpatient clinic setting, Tierney et al [22] tested the effects of a system of electronic 'suggestions' for cardiac care patients through a randomised controlled trial, and failed to demonstrate any control-intervention differences in quality of life, medication compliance, health care utilisation, costs, or satisfaction with care. The intervention had no effect on physicians' adherence to the care suggestions. However in Italy, electronic reminders have been shown to be effective in modifying prescribing behaviour. Filippi et al [23] investigated the effects of computerised reminders plus a letter describing the beneficial effects of anti-platelet therapy (intervention group) with the letter alone (controls) among 300 Italian general practitioners randomised to each group. The number of treated patients was significantly raised in the patients of the intervention group (OR 1.99, 95% CI 1.79 – 2.22).

In Scotland, the CARDIA (Computerised Automated Risk Detection Intervention and Advice) program [24] serves practices throughout Angus using a similar system of database integration as that proposed in this e-Nudge study. CARDIA interrogates the electronic health record (EHR), which uses information from both primary and secondary care sources. CARDIA targets resources by examining the practices' EHRs, identifying patients with existing cardiovascular disease (or those at high risk of it based on a Framingham calculation), and assesses the adequacy of care (e.g. drug therapy) in individual patients. However the effectiveness of this program has not been formally tested in a clinical trial.

In secondary care, Lilford et al [25] have described (but not evaluated) a system of electronic reminders for use in the antenatal clinic. This system supplies action suggestions during the antenatal booking interview, as a complement to individual clinical judgement. Eighty-two different suggestions were included in the software, and on average 1.5 of these were generated in an individual history. The authors emphasise the potential for such systems to be adapted to the resources and preferences of different hospitals.

#### **Controlled studies similar to the e-Nudge trial**

One randomised controlled trial in primary care [26] has assessed the effectiveness of electronic feedback using off-line data analysis followed by a flag in the electronic health record. Randomisation was at the health professional level. The outcome was the proportion of patients under the care of each professional still eligible for an alert a month later. This design is in some ways similar to this e-Nudge trial, and the result was positive, but it took place

in the USA and only involved one cycle of data analysis with follow-up one month later. In secondary care, the effectiveness of a similar intervention aimed at clinicians caring for hospital inpatients at risk of deep vein thrombosis (DVT) was more dramatically demonstrated [27]. In this case randomisation was at the individual patient level and the outcome was the actual development of DVT. The intervention group patients were found to have a 40% reduced rate of thrombosis compared with controls. A similarly-designed study of electronic reminders for the improved care of patients with HIV infection achieved a significant reduction in hospitalisation in the intervention group [28].

Mitchell et al [29] used information extracted from Scottish general practices to target care towards those aged 65–79 years most in need of intervention for their blood pressure. Information was extracted annually, and 54 practices were cluster-randomised into three groups: those receiving feedback of information identifying patients with uncontrolled blood pressure, those receiving the same feedback but including patients' estimated absolute cardiovascular risk, and control practices receiving no feedback. Whilst reductions in the proportion of patients with controlled blood pressure were seen, the results were compromised by difficulties in stratification according to practice characteristics (resulting in an excess of controls that were training practices, and having a hypertension recall system).

Evidence published to date suggests that the benefits of electronic reminders are context-dependent, relying not only on the area of care involved, but also on organisational parameters, clinical targets, and medicolegal implications. A Veterans Health Administration study [30] demonstrated significant variation in the implementation of electronic reminders including their greater use for conditions associated with performance measures. Agarwal et al [31], in a study of 15 different computerised reminders found that while overall adherence was high, there is significant variation by clinic, individual clinician and individual reminder. For instance, the hepatitis C risk assessment reminder was found to have the highest overall adherence rate (95.9%) and the tobacco use cessation had the lowest adherence rate (62.9%). Dickey et al [32] have reviewed the literature on a range of office based tools for improving behavioural change counselling in primary care. This included all types of tool, including electronic reminders. They found that no one type of tool or method of teamwork was consistently more effective than another, and identified the need for more high quality research, particularly in the area of health risk assessment and electronic reminder systems.

There is therefore mixed evidence supporting the effectiveness of electronic reminders and a need to confirm their ability to modify clinical behaviour in the particular context of UK primary care under the new GMS Contract.

### **Overview of study design**

This is a randomised controlled trial to test the effect of an automated electronic feedback system on CVD prevention in general practice. The practice populations over the age of 50 years will be randomised into two groups: "intervention" and "control". Intervention patients currently belonging to one of the high risk search groups described below will have alert messages appear on the screen when their electronic notes are opened. We will also apply an electronic search protocol every eight weeks to both groups throughout the study, to produce continually updated lists of potentially high risk patients for cardiovascular events. For the intervention group the patients on these lists will be revealed to the practice. The clinical software company EMIS, who serve the majority of practices in Warwickshire and Coventry, have programmed their software to produce the alerts and the eight-weekly lists for intervention patients. This "intervention" involves the feedback to practice teams to identify patients who are currently at high estimated risk, patients whose data is incomplete (who may benefit from updated measurements of cholesterol, blood glucose, blood pressure or recording of smoking status) and those who may have undiagnosed diabetes, through the alert messages and the eight-weekly lists. The control group will receive the usual care provided under the nGMS contract. No information will be withheld from the clinicians regarding control patients, the only difference will be the absence of reminders to draw their attention to the information. The practice teams themselves will decide on any changes in treatment in consultation with individual patients in both arms of the study, allowing care to remain tailored at the clinician-patient level. Outcomes will include the number of cardiovascular events and the number of high risk patients in the two populations (defined by inclusion on the eight-weekly search results). The design of the search protocol and the justification for the thresholds are described in the appendix.

### **Methods**

#### **Recruitment**

Up to twenty-six general practices in Coventry and Warwickshire who use EMIS LV software will be invited to participate in the trial. Dr Tim Holt will visit each practice to explain the trial and gain written consent from the general practitioners.

#### **Randomisation**

Participating practice patients over 50 years of age will be randomised into two groups – "intervention" and "con-

trol." Patients will be consistently allocated to these groups throughout the study using an electronic technique that is concealed to all researchers and practitioners involved. This process will occur electronically during each search, so that those who join the practice during the study will be randomised automatically as soon as they are first provided with electronic notes as a fully registered patient. Temporary residents are not included in the study.

#### **Applying the search strategy**

Alerts will be created automatically using patient information that is updated in real time and the search protocol described in Figures 1, 2, 3. For the eight-weekly lists we will apply the same search protocol to the databases of participating practices. This will produce lists for each practice of the high modifiable risk patients in the intervention arm of the study on the day of the search. The groups identified can be summarised as:

GROUP 1: Patients of all ages with existing cardiovascular disease or diabetes, whose blood pressure or cholesterol level is outside the QOF target range at the last estimation, or no "in date" level is recorded.

GROUP 2: Patients who are not known to have cardiovascular disease or diabetes, are *under* 75 yrs old, and whose risk profile is incomplete – more information is required to perform a risk estimate – but whose cardiovascular risk would be greater than 20% if the "assumed" values of the missing factors are used (see definition in appendix).

GROUP 3: Patients who are not known to have cardiovascular disease or diabetes, are *under* 75 yrs old, and whose most recent risk variable values indicate that their risk level is raised.

GROUP 4: Patients who are not known to have cardiovascular disease or diabetes, are *greater than* 75 yrs old and who have persistently elevated blood pressure based on the three most recent consecutive readings.

GROUP 5: Patients with possible undiagnosed diabetes on the basis of at least one previous high blood glucose record.

GROUP 6: Patients with CVD but not diabetes, who have not had a blood glucose measurement in the past three years.

Information on the "intervention" patients identified at each search is revealed to the practices. Information on the control patients including the number identified will be saved but no action will be triggered (Figure 4).

#### **Intervention – the "e-Nudge"**

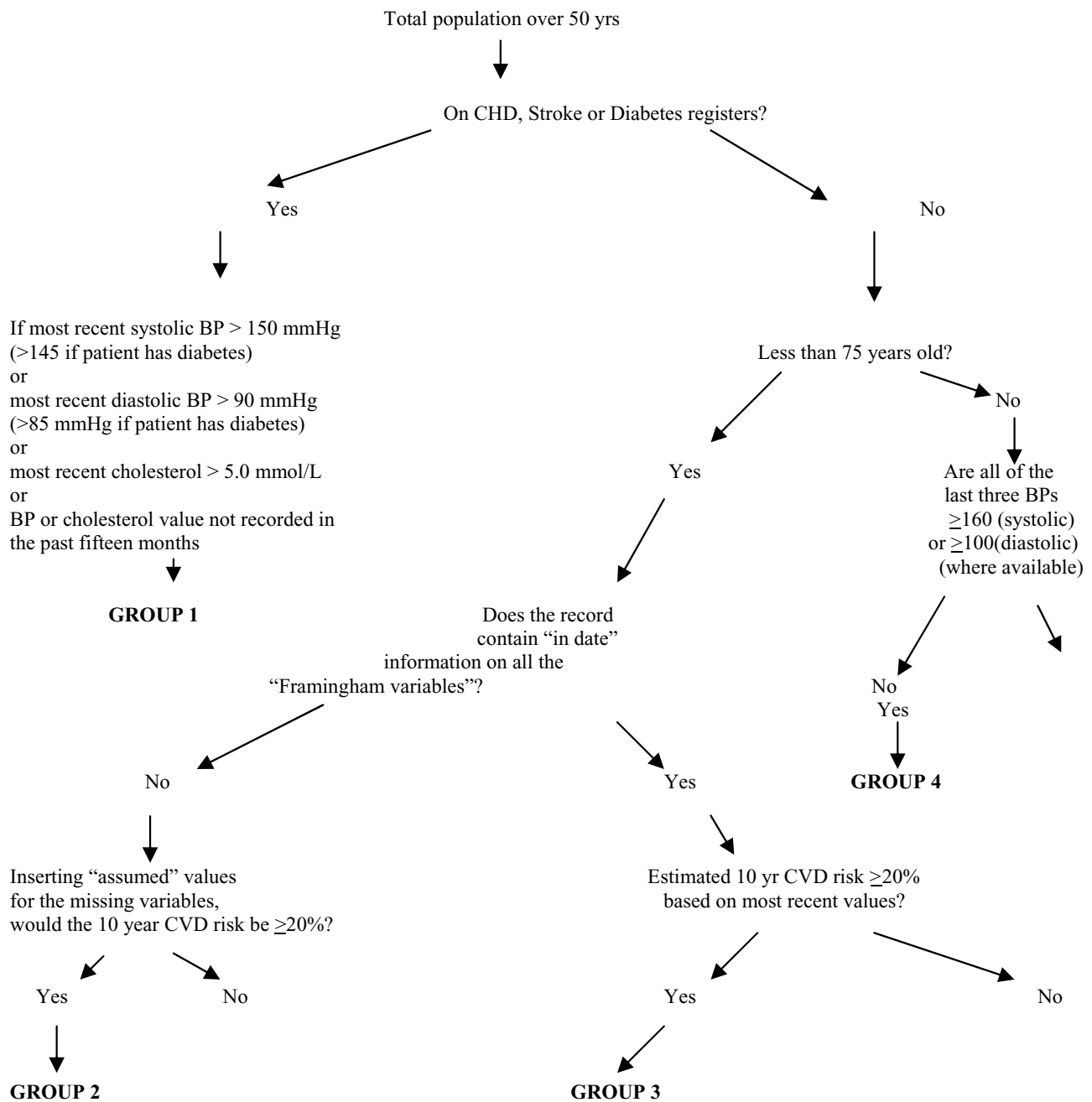
The e-Nudge is an automated feedback system that examines information already contained in practice databases to help practice teams target preventive interventions towards the individuals most likely to benefit. At the same time, the e-Nudge identifies clinically important missing risk variable values and patients with possible undiagnosed diabetes. Designed to run as a series of updated alert messages and searches that use most recent risk variable values, it is able to track practice populations over time as patients enter and leave the area, grow older, and enter practice disease registers, such as those for diabetes, CHD, or stroke. It recognises that risk profiles are dynamic, and that "one-off" estimates of risk in individuals are liable to become outdated [33].

The alert messages will arise automatically through EMIS software when a high risk patient's notes are opened, and are continuously updated in real time. To identify patients who may not present to the practice, electronic searches will be undertaken every eight weeks. The purpose of both alerts and the lists is to trigger awareness of individual patients' risk within the practice team, and not to dictate specific treatments. The "e-Nudge" is therefore simply the feedback of this information. The resulting action is at the discretion of the practice team, and can be tailored both to the time available, and to the needs and preferences of the individual patient in the context of the clinician's broader knowledge of co-morbidity, current medication, and past response to treatment. The practice teams will have the following notifications for intervention patients identified in the searches.

**1 The eight-weekly search result is presented to a nominated member of the primary care team under the six group headings.**

**2 Alert messages** are displayed automatically on the computer screen each time the patients' electronic notes are opened. These are triggered for those identified in any of the groups:

- Group 1 patients: *This CHD/Stroke/Diabetes (state which) patient's (BP) or (serum cholesterol) level (specify which) is out of the target range.*
- Group 2 patients: *This patient may be at high cardiovascular risk, but values for the following risk variables were either missing or out of date: (specify which variables).*
- Group 3 patients: *This patient's estimated cardiovascular risk may be elevated, based on the most recent risk variable values. (State assumptions made)*

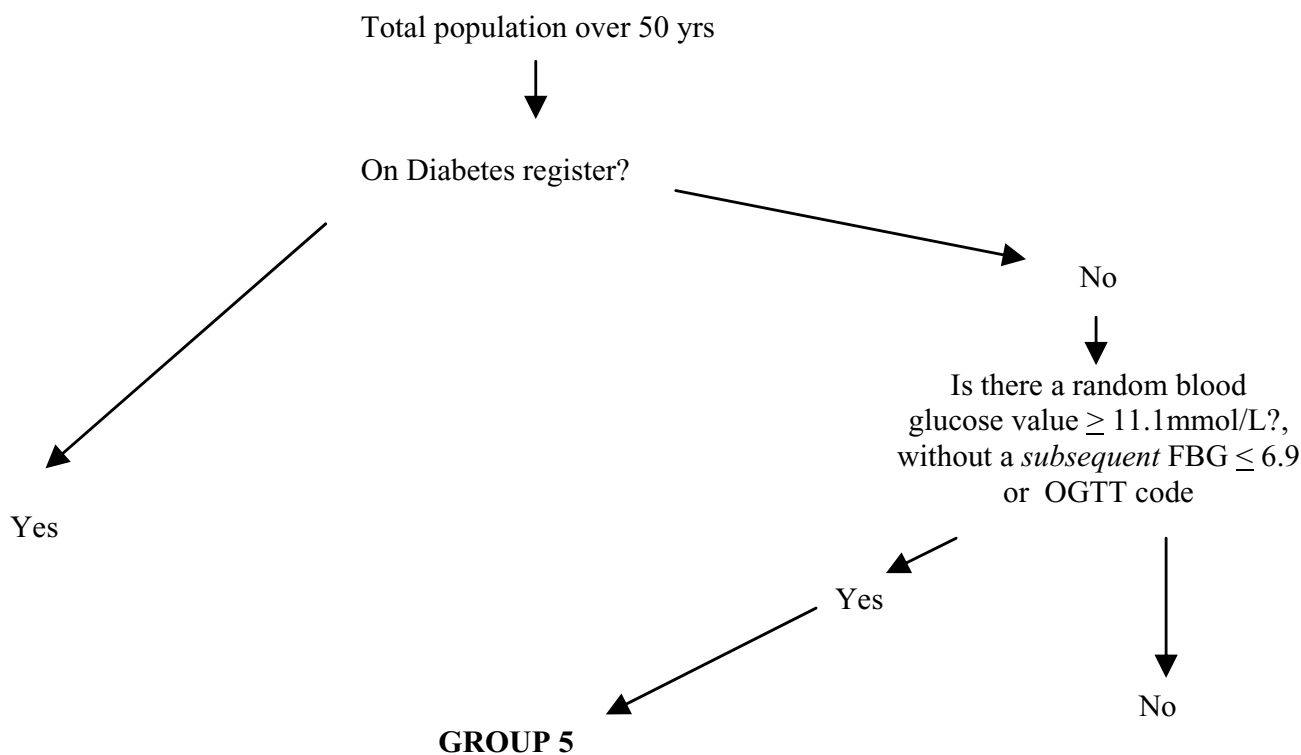


**Figure 1**

Search algorithm to identify those most likely to benefit from cardiovascular prevention based on recent risk variable values. Definitions for terms in inverted commas are given in the appendix along with justification of thresholds and search protocol.

• Group 4 patients: *This patient's blood pressure is persistently elevated based on three consecutive values.*

• Group 5 patients: *This patient may have undiagnosed diabetes, based on a previous raised blood glucose level ≥ 11.1 mmol/L.*



**Figure 2**  
Identification of Group 5.

- Group 6 patients: *This CHD/Stroke patient (state which) has no recorded blood glucose measurement in the past three years.*

#### Control condition

Control patients at high estimated risk will be identified but the practice teams will not be provided with these extra reminders, although the team will have access to all the clinical information used to assess risk status. Control patients will continue to receive the usual care provided by current general practice under the nGMS contract. Some practices have started to use alerts for CVD or Diabetes patients who are out of the nGMS blood pressure and cholesterol targets since this study was conceived. Where this is now 'usual care,' this part of the intervention (Group 1 alerts) will not be withheld from the control patients, but the rest of the e-Nudge (including identification on the eight-weekly searches) will be. The standard of care is high in the study locality [South Warwickshire Primary Care Trust, QOF data on file], providing a suitable environment to test the e-Nudge. If the study shows a positive effect, this will demonstrate that even good care can be improved, and it is anticipated that the tool will be

even more effective in environments where care is of a lower standard.

#### Ethical approval

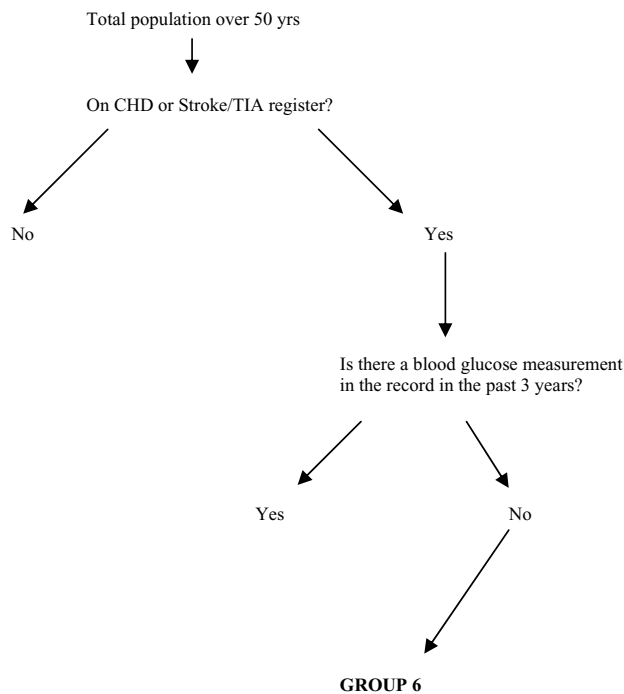
The trial has been developed in accordance with the Declaration of Helsinki, and approved by Warwickshire Local Research Ethics Committee (Ref: 05/Q2803/85).

#### Outcome analysis

The searches and alerts will continue for a period of two years, at the end of which the data will be examined. We will continue to collect and analyse data on the primary and secondary outcomes of the study for a further year after this. Outcomes will be measured using searches on practice databases. Analysis will be undertaken on an "Intention To Treat" basis within practices. Practices that withdraw will have their data censored from the date of withdrawal from the trial.

#### Primary outcome

Difference in the annual incidence rate of cardiovascular events (see definition in the appendix) in the intervention and control populations during the two years of the study,



**Figure 3**  
Identification of Group 6.

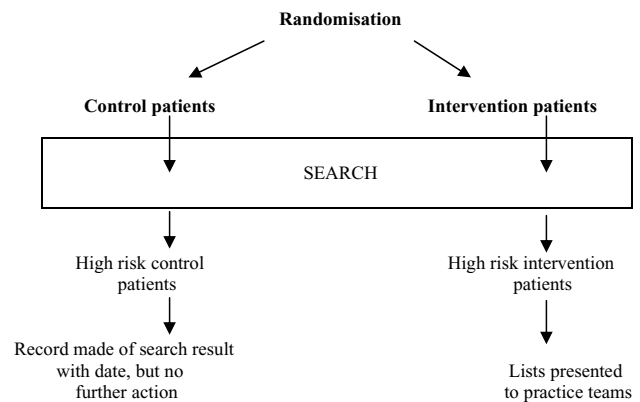
and for a third year following the end of the e-Nudge intervention.

#### Secondary outcomes

- Difference in the proportion of high risk patients (Groups 1, 3 and 4) identified in the control and intervention populations averaged over the last three searches in the two year intervention period, and in the third year following the end of the intervention.
- Difference in the proportion of patients in each population identified with missing data (Groups 2 and 6) averaged over the last three searches in the two year intervention period, and in the third year following the end of the intervention.
- Difference in the proportion of patients with undefined diabetes status (i.e. raised blood glucose levels with no diagnosis of diabetes and no FBG or OGTT results to confirm status) (Group 5) in the intervention and control populations averaged over the last three searches in the two year intervention period, and in the third year following the end of the intervention.

#### Statistical analysis

Analysis of the data will be carried out in STATA. The principle analyses will be on an intention-to-treat basis and



**Figure 4**  
Eight-weekly searches on practice databases.

will be performed using the CONSORT guidelines (2001) [34].

#### Data monitoring committee

Outcomes will be assessed annually during the study by an independent data monitoring committee, who will inform the trial investigators if the trial should terminate early on ethical grounds due to a 20% difference in mortality or morbidity between the intervention and control groups.

#### Data quality assurance measures

We will examine the cause of death of every patient in the practices over age 50 years who dies during the study, to ensure that all cardiovascular deaths are recorded appropriately in searchable form prior to outcome data extraction. Any patient recorded as having more than one cardiovascular event during the study will have their clinical record examined, to identify patients who have had the same event recorded twice (which may happen when a consultation for a stroke, TIA or myocardial infarction is mistakenly labelled as a "new episode" rather than a "review"). This process will be carried out both on controls and intervention patients. In addition, we will examine the notes of any patient who has a record of an event dated within 4 months of registration with a practice, in case this event occurred in the past but was incorrectly dated when the patient registered.

#### Sample size calculation

##### Event rates

Our study defines a cardiovascular event as a new diagnosis of CVD, a new myocardial infarction, a new stroke, a new transient ischaemic attack, or sudden death from CVD. A new stroke in someone with a previous stroke will

count as a new event. An acute myocardial infarction in a patient previously diagnosed with angina will be recorded as a new event, but a new onset of angina in a patient who already had a diagnosis of acute myocardial infarction might not be recorded as a new diagnosis, as the patient will already be on the CHD register.

The British Heart Foundation [35] has compiled an estimate of the number of cardiac events in the UK population in 2002 from several available data sources. The number of myocardial infarctions (all ages) was estimated to be 268,000, while the number of new cases of angina (all ages) was estimated to be 338,000

The UK population was 59,321,700 in 2002 [Sources: Office for National Statistics, General Register Office for Scotland, Northern Ireland Statistics and Research Agency], so estimated incidence rates for coronary heart disease are

**Incidence of myocardial infarction** 451.77 per 100,000

**Incidence of new case of angina** 569.77 per 100,000

For *cerebrovascular disease*, the OXVASC study [36] provides a local source of information drawn from an Oxfordshire population. The incidence rates were:

**Incidence of stroke** 187 per 100,000

**Incidence of TIA** 51 per 100,000

Therefore

**Incidence of all cardiovascular events** 1260 per 100,000

*Clinical significance*

We aim to demonstrate at least a 10% reduction in the cardiovascular event rate. This means that for a positive outcome, the event rate in the intervention population must be ≤90% of the event rate in the control population. We therefore estimated the necessary sample size for this reduction to be detected at the 5% level with 80% power.

*Estimating population size needed*

A Poisson distribution model is appropriate for events that are rare on an individual level, occurring randomly and independently at a constant rate in a population [37].

Assuming a Poisson distribution, the formula for the sample size is:

$$N = \frac{[z_{1-\alpha}\sqrt{\lambda_0} + z_{1-\beta}\sqrt{(\lambda_0 + \delta)}]^2}{\delta^2}$$

where:

$\lambda_0$  = the expected incidence of cardiovascular events (i.e. 1260/100,000)

$\delta$  = new incidence in the intervention group

$z_{1-\alpha}$  = standardised normal distribution value based on 0.05 significance level

$z_{1-\beta}$  = standardised normal distribution values for 80% power

$N$  = total number of patients required in the study

$Nw$  = total number of patients required in the study + 10% to account for practice withdrawal

For 80% power and 0.05 significance level (2-tailed) [38] (see Table 1):

The practice population required to detect both statistically and clinically significant changes in the cardiovascular event rate is therefore estimated to be approximately **70,000**, the combined list size of all age groups in participating practices.

**Discussion**

We have described the protocol of our trial of an electronic reminder system (the e-Nudge) that aims to change general practitioners' behaviour with respect to patients at risk of CVD. The trial will use routinely collected electronic data to repeatedly flag up high-risk patients and will measure the outcomes in terms of cardiovascular event rates and the risk profile of the over-50 year population. Electronic alert messages are now commonly used in the increasingly integrated software environment of UK primary care, but the evidence to support them is inconclusive. This trial will attempt to provide a more robust evidence base for the use of such tools for preventive care in UK general practice.

**Table 1:**

Reduction in incidence (%)	$z_{1-\alpha}$	$z_{1-\beta}$	$\lambda_0$	$\delta$	$N$	$Nw$
10	1.96	0.8416	0.0126	0.001260	64133.46	70546.80



Operational issues that arose during the design of this project included those of data quality and software interoperability. Because the coding of clinical data under the nGMS is linked to remunerative targets, a widespread standardisation of Read coding has occurred since 2004 in areas of care related to chronic disease management. Without this development it is doubtful that a trial of this design could be conducted. Despite this, the use of alternative codes within the nGMS contract for data such as blood glucose values made the programming of the search algorithm challenging, particularly as more than one hospital laboratory (which generate these data for practices through electronic links) are involved in the study area. The identification of individual patients' smoking status was designed with current recording practice in mind, and this area of the program was the least secure in terms of accuracy, as it is not always possible to determine from electronic records exactly how long ago an ex-smoker quit. Participating clinicians are made aware of the limitations of this part of the program so that adjustments can be made based on a knowledge of the patient's actual smoking history.

The e-Nudge Trial is an example of a new model of primary care research. It involves the flow of information out of the databases of participating practices to the practising teams, to then influence clinical behaviour and future data patterns. The search techniques involved include not only the identification of patients according to the presence in their notes of coded data, but a *computation* (using in this case the Framingham CVD algorithm) to define a more complex decision boundary between the high risk and low risk patients in a live database. This approach has become necessary in the light of the most recent guidelines on the prevention of cardiovascular disease [4], which explicitly support the definition of the hypertensive and hyperlipidaemic populations according to overall cardiovascular risk, estimated using both risk algorithms and other information known to the clinician. Such algorithms might lend themselves to future adaptation, by broadening the range of input risk variables, the use of alternative statistical models for the classification of high risk groups, and tailoring to regional populations [33].

The appendices describe the evidence behind the choices made in designing the study including thresholds, assumed values, and definitions.

## Appendices

1. Justification for the thresholds and search protocols used in the study

a) Age group

b) The high CVD risk group (Group 3)

2. Identifying patients with undiagnosed diabetes

3. Screening for type 2 diabetes in populations at risk of CVD

4. Search groups 1, 3 and 4

5. Definitions:

a) "In date"

b) "Framingham variables"

c) "Assumed values"

d) "Cardiovascular event"

### ***1. Justification for the thresholds and search protocols used in the study***

#### ***a) Age group***

We decided to include in the searches only those patients over 50 yrs, as the prevalence of cardiovascular disease begins to climb steeply at this age [35]. As the main outcome involves a comparison of the effect of the intervention on event rates, this will avoid the dilution of each denominator population by low risk patients.

#### ***b) The high CVD risk group (Group 3)***

The group at high risk of CVD (but who do not already have CHD, Stroke/TIA, or Diabetes) is defined not by a simple combination of diagnostic categories, but as the output of a risk prediction algorithm. The Framingham study data [39] is currently the best available source for patients without CVD under 75 years, and is recommended in the CHD NSF [3] and the 2004 British Hypertension Society Guidelines [40], despite some concern over its applicability to the UK population [41]. We will be using the *most recent values* as inputs for this algorithm. Whilst the recommended approach is to use values prior to treatment with antihypertensive or lipid lowering therapy, our approach is similar to that applied to individuals in existing prediction tools [42,43] that can compare "pre-treatment" with "post-treatment" risk, to emphasise the impact on risk of intervention such as drug therapy and lifestyle modification. We are therefore making no distinction between the estimated risk levels of two patients with identical risk profiles including blood pressure, one of whom is on antihypertensive treatment and the other is not. In fact the treated patient, whilst having a significantly lower cardiovascular risk than before commencing therapy, still has a higher risk (not recognised by our search protocol) than the otherwise similar patient with the same blood pressure not requiring therapy. Despite this limitation, this approach is currently the most effective means of utilising primary care data (where "pre-

treatment" blood pressure or lipid levels are often not identifiable), and is very much in keeping with the monitoring process of the QOF, which measures performance according to the most recent values of variables such as blood pressure or serum cholesterol.

## 2. Identifying patients with undiagnosed diabetes

The application of these searches provides an opportunity to identify patients who may have undiagnosed diabetes. Such searches have been shown to include patients absent from diabetes registers with blood glucose measurements above the usual diagnostic threshold of 11.1 mmol/L. For instance, the Diabetes Audit and Research in Tayside Scotland (DARTS) study [44] identified 701 patients with isolated hyperglycaemia in a number of primary and secondary care registers, from a population of 391 274. This figure was 9.2% of the 7596 identified with diabetes. Whilst such patients (particularly if asymptomatic) require further investigation to clarify their diabetes status [45], a number may benefit through earlier detection and treatment if diabetes is confirmed. During pilot work in one local practice, a search identified the following (see Table 2):

Of these six:

1. Four patients had undiagnosed type 2 diabetes later confirmed by fasting blood glucose measurements.
2. One patient had impaired fasting glycaemia (FBG 6.9 mmol/L) and is awaiting further investigation with OGTT to exclude diabetes.
3. One patient had probable steroid induced hyperglycaemia and has had a normal blood glucose value recorded since stopping the steroids.

We are therefore including as part of the regular searches a query to identify such patients, who may have undiagnosed diabetes based on previous raised measurements. Such patients identified in this study will need to have a subsequent non-diabetic fasting blood glucose level ( $\leq 6.9$  mmol/L) or Oral Glucose Tolerance Test in order that future searches classify them as not having diabetes (see also appendix 5 below). Some of these patients in whom diabetes appears to be refuted by fasting measurements may go on to have further abnormal plasma glucose levels, in which case they will again be identified as possible

cases (Group 5) until a further normal fasting glucose level is obtained, or a diagnosis of diabetes is made.

## 3. Screening for type 2 diabetes in populations at risk of CVD

Diabetes UK has issued a position statement on the early identification of people with type 2 diabetes [46]. Among other groups, this document identifies people with ischaemic heart disease, cerebrovascular disease, peripheral vascular disease or hypertension as high risk groups justifying screening, with a screening interval of three years. However a reliable and practical screening test has not been established. Whilst fasting plasma glucose estimation is significantly more specific than random plasma glucose estimation, it is less practical. In addition to the detection of possibly undiagnosed patients described above, we have therefore designed the study to encourage blood glucose testing at least every three years in groups who either have, or who are at high risk of CVD. These tests can be carried out during the routine blood checks that patients receive for monitoring of lipid lowering or anti-hypertensive therapies. Therefore negative diabetes status will only be assumed if the patient is not on the Diabetes register *and* a normal plasma glucose level (random or fasting) is present in the record within the three years prior to the search. We will be allowing the follow up of patients with borderline plasma glucose levels to remain at the discretion of the practices. (The recently published Joint British Societies guidelines on prevention of cardiovascular disease in clinical practice (JBS 2), clarifies currently recommended practice in this area for the first time [4].) This study may be able to determine whether this approach is useful as a means of detecting type 2 diabetes earlier in these groups, given its practicality and low cost. Practices are at liberty to use more specific screening tests on any individual whom they feel justifies it.

## 4. Search groups 1, 3 and 4

The Group 1 patients are identified on the basis of thresholds used as audit targets in the nGMS contract for secondary prevention. Whilst these treatment targets are essentially arbitrary [47], they have been selected through extensive discussions between the Department of Health and expert advisory bodies. Following advice in the National Service Framework for Diabetes [48] and supported by the 2004 BHS guidelines [40] and JBS 2 [4], the nGMS QOF recommends that patients with diabetes are treated as if they already have cardiovascular disease in terms of cholesterol and blood pressure control. The latter in fact requires tighter target levels than for patients with CVD alone. For this reason they will similarly be regarded as secondary prevention patients in this study.

For primary prevention (Group 3 and Group 4), the British Hypertension Society Guidelines (2004) recommend

**Table 2:**

Currently registered patients:	12,245
Plasma glucose on record $\geq 11.1$ mmol/L but no diagnosis of diabetes	6

a 10-year risk of developing cardiovascular disease of  $\geq 20\%$  as a threshold for treatment of grade I hypertension with antihypertensive drugs, or lipid lowering therapy in all groups at this risk level up to the age of 80 yrs [40]. However, the Framingham algorithm is not designed to be used in patients over 75 years of age, and the CHD NSF [3] recommends that the systematic identification of new primary prevention candidates (particularly for lipid lowering therapy) should stop at age 74 years. However, older hypertensive patients benefit from blood pressure reduction and the identification of patients with grade II hypertension or higher, based on serially elevated blood pressure measurements can therefore be justified above this age limit. Whilst it might be justifiable to reduce this threshold (for instance to identify older patients with grade I rather than grade II hypertension), this would involve identifying potentially large numbers of patients whose need for treatment was not as clear, adding considerably to the workload involved.

### 5. Definitions

5a "In date" means:

1. A blood pressure reading within the last fifteen months for patients who have CHD/Stroke/TIA or Diabetes, otherwise three years.
2. A blood glucose level within the last three years (for those without diabetes).
3. A cholesterol level in the last fifteen months for CHD, Stroke/TIA or Diabetes patients, and three years for non-CHD/Stroke/TIA, non-Diabetes patients (applies to possible Group 2 patients, see next section).

5b "Framingham variables", in this study means:

1. Age
2. Sex
3. Smoking status (considered positive if record of smoking tobacco at last use of this Read code group, however long ago). A *previously recorded* smoker who has stopped will be considered a non-smoker only if 1 year has elapsed since quitting. Therefore a "smoker" is anyone who has smoked tobacco regularly in the past 1 year.
4. Systolic blood pressure – average of last three "in date" values if available. If there are fewer measurements available, then the average of these is taken.
5. Total serum cholesterol at most recent measurement, if "in date"

6. Serum HDL cholesterol – as for total cholesterol

7. Left Ventricular Hypertrophy status – assume negative unless there is any positive electronic record of LVH.

8. Diabetes status, according to whether or not the patient is on the Diabetes register. However, as discussed above, this depends on the quality of such registers. If a primary prevention patient less than 75 yrs does not have a diagnosis of diabetes, but there is no blood glucose level "in date" (i.e. in the past three years), then the risk algorithm will base the risk calculation on an assumption of *positive* Diabetes status, and if the risk level is then high, the practice will be notified with this assumption stated, as a Group 2 Alert message. If a patient (this time including those above 75 yrs) is not on the Diabetes register but there is a record of a blood glucose level greater than or equal to 11.1 mmol/L, then the practices will be notified for clarification, regardless of the patient's CHD/Stroke status or calculated risk level as a Group 5 patient. The matter can be clarified by the practice teams if they wish, by organising a Fasting Blood Glucose (FBG) or Oral Glucose Tolerance Test (OGTT). A FBG  $\leq 6.9$  mmol/L or OGTT code following (at a later date to) the high random blood glucose level will mean that the patient is no longer in Group 5 (but may re-enter it if further raised blood glucose levels occur). The FBG or OGTT must be clearly recorded electronically by the practices using appropriate codes (to distinguish fasting values from random blood glucose values), or the patient will continue to be flagged up in subsequent searches. If, despite a normal FBG result or OGTT, a *further* raised random value subsequently occurs ( $\geq 11.1$  mmol/L) then once again the program will question whether or not the patient has diabetes by including them in Group 5, until a *further* FBG  $\leq 6.9$  or OGTT code is recorded, or the patient is diagnosed and added to the Diabetes register.

5c "Assumed values" for the missing variables means:

1. For systolic blood pressure: Male 135 mmHg, Female 132 mmHg
2. For total serum cholesterol: Male 5.7 mmol/L, Female 6.2 mmol/L
3. For HDL cholesterol: Male 1.4 mmol/L, Female 1.7 mmol/L
4. For diabetes: positive status.
5. For smoking status: non-smoker.

These blood pressure and cholesterol thresholds are the approximate median or mean values in the 50–74 year

age group taken from the Health Survey for England 2003 [49].

5d A "cardiovascular event" is defined as:

1. A new diagnosis of cardiovascular disease (i.e. entry onto the CHD or Stroke/TIA registers)
2. A new stroke or transient ischaemic attack (TIA) (whether or not already on the Stroke register)
3. A new myocardial infarction (whether or not already on the CHD register).
4. Sudden death from cardiovascular disease.

### Abbreviations

CVD Cardiovascular disease

CHD Coronary heart disease

TIA Transient ischaemic attack

DVT Deep vein thrombosis

nGMS The new General Medical Services contract in UK primary care

QOF Quality and Outcomes Framework of the nGMS

BHS British Hypertension Society

JBS 2 The second report of the Joint British Societies on the prevention of cardiovascular disease in clinical practice

EHR Electronic health record

FBG Fasting blood glucose

OGTT Oral glucose tolerance test

LVH Left ventricular hypertrophy

### Competing interests

The author(s) declare that they have no competing interests.

### Authors' contributions

TH is the Principal Investigator and takes responsibility for the day to day running of the trial. MT is the Chief Investigator. MT and FG have assisted in the design of the trial and the development of the protocol. SM has advised on the implementation issues through the local Primary

Care Trusts and general practices. All authors have contributed to the drafting of this article.

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# Identifying individuals for primary cardiovascular disease prevention in UK general practice: priorities and resource implications

Tim A Holt, Margaret Thorogood, Frances Griffiths, Stephen Munday and David Stables

## ABSTRACT

Targeted cardiovascular disease prevention relies on risk-factor information held in primary care records. A risk algorithm, the 'e-Nudge', was applied to data from a population of  $\geq 50$ -year-olds in 19 West Midlands practices, to identify those individuals at risk of cardiovascular disease. Altogether, 5.9% were identified aged 50–74 years at  $\geq 20\%$  10-year risk based on existing data, and a further 26.4% were potentially at risk but had missing risk-factor information; 9.2% of patients aged over 50 years with established cardiovascular disease had at least one modifiable risk factor outside the audit target of the Quality and Outcomes Framework. Implications for resource allocation are discussed.

### Keywords

algorithms; cardiovascular diseases; medical informatics; medical record systems, computerised; risk assessment; risk factors.

## INTRODUCTION

Current UK guidelines recommend that individuals at  $\geq 20\%$  risk of cardiovascular disease over the next 10 years should be identified for primary prevention interventions,<sup>1–3</sup> including lipid-lowering therapy. However, such activity is not commissioned through the Quality and Outcomes Framework (QOF),<sup>4</sup> and practice teams must balance the resource implications against other priorities, including the care of those with established cardiovascular disease.

The identification of individuals at risk is assisted by the 'e-Nudge' software tool, developed by the current research team and programmed by EMIS, to identify individuals likely to justify either intervention or further assessment of cardiovascular risk. The e-Nudge tool is an automated system of continually updated searches and screen alerts currently under trial. Its name reflects the role of the software to act as a subtle prompt in consultations to support cardiovascular disease prevention during routine care. The aim of the current survey was to compare the proportions of individuals identified in different risk categories, and discuss the implications for routine practice.

In addition to the practical challenge of fitting risk assessments into busy practice, there is concern over identifying cardiovascular risk in older individuals that may be attributable largely to non-modifiable factors.<sup>5,6</sup> This study reports the proportion of the population aged 50 years and over identified, using the e-Nudge algorithm, as at  $\geq 20\%$  risk, the proportion who may be at risk but have missing risk factor information, and the proportion with diagnosed cardiovascular disease or diabetes who have at least one modifiable risk factor outside of the audit target of the QOF.

## METHOD

The e-Nudge tool identifies several groups of patients based on clinical variables and the availability of risk-factor information in the practice database. It also identifies individuals with

TA Holt, MRCP, FRCGP, clinical lecturer;  
M Thorogood, PhD, FFPH, professor of epidemiology;  
F Griffiths, PhD, FRCGP, reader, Health Services Research Institute, Warwick Medical School, Coventry; S Munday, MRCP, FFPHM, Director of Public Health, Solihull NHS Care Trust; D Stables, MB ChB, medical director, Egton Medical Information Systems, Leeds.

### Address for correspondence

Dr TA Holt, Health Services Research Institute, Warwick Medical School, Gibbet Hill Road, Coventry, CV4 7AL.  
E-mail: tim.holt@warwick.ac.uk

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## How this fits in

Despite recent improvements in the recording of cardiovascular risk factor data in primary care, for every individual with complete risk factor information, there are perhaps four or five in the practice who would require further data collection. They are also outnumbered by individuals with established cardiovascular disease whose risk factors are both uncontrolled and modifiable.

insufficient recorded information for a risk estimate. For those with sufficient data and no diagnosis of cardiovascular disease or diabetes, it estimates cardiovascular risk using the Framingham cardiovascular disease equation.<sup>7</sup> Details of its structure are published elsewhere.<sup>8</sup>

It takes into account an average of up to three systolic blood-pressure values in the past 3 years, and the most recent total and high-density lipoprotein cholesterol levels. Where information is missing, dummy values are inserted to calculate a potential risk score. When smoking status is unknown, the patient is assumed to be a non-smoker. Where blood-pressure or cholesterol values are missing, the algorithm uses median values of the 50–74-year-old group from the Health Survey for England 2003.<sup>9</sup>

As glucose testing is important in cardiovascular risk assessment, the e-Nudge tool assumes a positive diabetes status for those aged 50–74 years who are not on the diabetes register and have had no blood-glucose measurement in the past 3 years, and calculates the Framingham cardiovascular disease risk. If this is  $\geq 20\%$ , the individual is identified as being in the group requiring further data collection. This information helps to target those most likely to benefit from testing for diabetes. The Framingham equation was not

applied to those with known diabetes or cardiovascular disease, but in these groups it identifies those outside the QOF audit targets for blood pressure and/or total cholesterol level.

The e-Nudge software was installed in 19 general practices in north and south Warwickshire, Coventry, and Rugby as part of a randomised controlled trial of it.<sup>8</sup> After installation, baseline data on the proportion of the population identified in the various categories were extracted to provide the data for this survey. These provide information on the levels of data available to support a programme of primary cardiovascular disease prevention and the likely workload implications for general practice. For the primary prevention group, all individuals above the risk threshold of  $\geq 20\%$  are flagged up, with no stratification of risk above this level. The age of the patient is known to the clinician during the consultation but there is no breakdown by age of identified individuals in this survey.

## RESULTS

The 19 practices had a total list size of approximately 121 000, with 36 546 patients aged  $\geq 50$  years. Median list size was 5200 (ranging between  $<2000$  and  $>12\,000$ ). Age structure closely matched that of the UK population and all quartiles of the English Index of Multiple Deprivation were represented. Based on the Super Output Areas of the practice postcodes, the coronary heart disease standardised mortality ratios ranged from 74 to 110.

Altogether, 5.9% of the population aged  $\geq 50$  years were identified as aged 50–74 years and with  $\geq 20\%$  cardiovascular disease risk based on existing data; 26.4% were aged 50–74 years and possibly at risk, but some risk-factor information was missing, and 9.2% aged over 50 years (no upper age limit) were already diagnosed with cardiovascular disease or with diabetes, but had a total serum cholesterol or blood-pressure measurement out of the QOF audit target range for the relevant group (Table 1). Some patients identified were already on treatment for at least one risk factor but remained at  $\geq 20\%$  estimated risk, with the potential in some cases to benefit from further risk reduction.

## DISCUSSION

### Summary of main findings

This study demonstrates that primary care data may be combined with practice-based software to identify individuals at risk of cardiovascular disease. Around 6% of the population aged  $\geq 50$  years and  $<75$  years, appears to be at raised risk ( $\geq 20\%$ )

**Table 1. Numbers and proportions of patients identified in each risk category (aggregated data from all 19 practices).**

Group definition	Number identified	Proportion of population aged $\geq 50$ years (%)
Patients aged 50–74 years at $\geq 20\%$ cardiovascular risk based on existing data	2152	5.9
Patients aged 50–74 years with missing risk factor information who would be at $\geq 20\%$ risk when assumed values are inserted (see Method)	9657	26.4
Patients aged $\geq 50$ years with known cardiovascular disease or diabetes whose blood pressure or cholesterol level was not in target in the past 15 months (Quality and Outcomes Framework audit target)	3346	9.2

<sup>a</sup>Total number of patients = 36 546

based on existing data. In some cases, raised risk was only apparent when a number of factors were combined, demonstrating the potential for the software to assist practitioners in determining actual risk (Box 1, Case 1).

### Strengths and limitations of the study

This survey involved a range of practices from urban, suburban, and rural environments, and used 'live' data collected during routine practice. However, there are a number of problems with this approach: pre-treatment values of blood pressure and lipids are not always available, and e-Nudge uses the most recent values; risk may be underestimated in some cases as the Framingham risk equation, on which the e-Nudge is based, should ideally use pre-treatment values; as a case-finding tool, this limitation increases its specificity at the expense of some sensitivity.

The e-Nudge tool is designed to assist practice teams that may then assess individual risk based on the broader context, including risk factors such as ethnicity, obesity, waist circumference, family history, and deprivation. An age cut-off of 50 years was chosen for the e-Nudge randomised controlled trial,<sup>7</sup> as the outcomes will include cardiovascular events that are more common above this age; this threshold was used in the current survey. If patients aged 40–49 years, who are at lower overall risk, were included, the number of patients requiring intervention would increase, although the proportion of the population that was identified would fall.

Unknown diabetes status accounts for the relatively high number of people that were identified with no recent glucose value on record but who would get a high Framingham risk score if a positive input was assumed for their diabetes status. This is a pragmatic manoeuvre to avoid identifying the entire population of those aged  $\geq 50$  years who have no recent blood-glucose level on record, many of whom will be at low estimated risk. This compromise allows a user of e-Nudge to identify the patients most likely (from a cardiovascular disease risk-profiling perspective) to benefit from blood glucose testing. The use of 'assumed' values for missing data is a common technique but may have a significant detrimental effect on the effectiveness of a screening programme.<sup>10</sup>

There are also problems with basing risk calculations on single risk-factor values. Although e-Nudge uses an average of up to three systolic blood-pressure measurements, it uses only single values for cholesterol levels (as commonly occurs in clinical practice). At the 20% threshold,

95% confidence intervals for cholesterol values may produce a range of risk estimates from 14% to 26%.<sup>11</sup>

### Comparison with existing literature

Studies using cardiovascular disease risk algorithms applied to primary care data include those of Muir *et al*,<sup>12</sup> Mitchell *et al*,<sup>13</sup> and Marshall.<sup>14</sup> However, all of these studies used data collected before the introduction of the QOF, which led to a widespread standardisation of electronic coding of cardiovascular risk factors. More recently, a new cardiovascular risk algorithm (QRISK) has been developed based on this approach.<sup>15</sup> This study by Hippisley-Cox *et al* found that 13% of the 35–74-year-old age group would be at  $\geq 20\%$  risk according to the Framingham algorithm. This is a higher figure than the 6% found in the present study, mainly because the QRISK figure (using a different denominator population) includes those patients with substituted values for missing risk-factor data. The figure in the present study for the 'incomplete data but potentially at risk' group

### Box 1. Vignettes of patients at risk of cardiovascular disease.

#### ► Case 1

- A 50-year-old male
- Smoker
- Average of recent systolic blood pressures = 140 mmHg
- Total cholesterol = 4.6 mmol/l
- High-density lipoprotein (HDL) cholesterol = 0.8 mmol/l

This person has modifiable risk factors: as well as help with stopping smoking, his cholesterol ratio might be improved through drug therapy and dietary advice. However, he might be difficult to spot as 'at-risk of cardiovascular disease' without help from the software, as his blood pressure and total cholesterol are not particularly high.

#### ► Case 2

- A 74-year-old male
- Non-smoker
- Average of recent systolic blood pressures = 145 mmHg
- Total cholesterol = 5.2 mmol/l
- HDL cholesterol = 1.3 mmol/l

It will be more difficult to modify this patient's risk, as his age is a significant factor. However, his blood pressure might justify treatment under current guidelines if it remains in the range 140–159 mmHg, and his lipid profile might also be further improved.

Either of these people might benefit from modification of the other factors not included in the risk algorithm, such as physical activity, weight, and waist circumference. Both justify low-dose aspirin therapy.



(26.4%) is higher because of the 'uncertain diabetes status' described above.

### **Implications for future research and clinical practice**

Current guidelines recommend that those with a  $\geq 20\%$  10-year risk of cardiovascular disease should be treated and followed up with a similar priority to those with established disease.<sup>2</sup> For every individual with complete risk-factor information, there are perhaps four or five in the practice who would require further data collection. This additional investigation implies a considerable resource commitment, although risk stratification might optimise this process.<sup>14</sup>

Individuals identified include those whose risk is difficult to modify (Box 1, Case 2). At the same time, secondary prevention patients with uncontrolled but more clearly modifiable risk factors are also easy to identify. Such patients are already labelled with a significant medical problem and are usually already used to taking drug therapy. It is hoped that the current randomised controlled trial of the e-Nudge software<sup>8</sup> will provide further evidence on

the feasibility of primary cardiovascular disease prevention as part of routine care in UK general practice.

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### **Ethical approval**

Ethical approval was granted by Warwickshire LREC, reference 05/Q2803/85

### **Competing interests**

The authors have stated that there are none.

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# Identifying undiagnosed diabetes: cross-sectional survey of 3.6 million patients' electronic records

Tim A Holt, David Stables, Julia Hippisley-Cox, Shaun O'Hanlon and Azeem Majeed

## ABSTRACT

### Background

Around 1% of the UK population has diabetes that is either undiagnosed or unrecorded on practice disease registers.

### Aim

To estimate the number of people in UK primary care databases with biochemical evidence of undiagnosed diabetes. To develop simple practice-based search techniques to support early recognition of diabetes.

### Design of study

Cross-sectional survey of 3 630 296 electronic records.

### Setting

Four hundred and eighty UK practices contributing to the QRESEARCH database.

### Method

Electronic searches to identify people with no diabetes diagnosis in one of two categories (A and B), using the most recently recorded blood glucose measurement: random blood glucose level  $\geq 11.1$  mmol/l or fasting blood glucose level  $\geq 7.0$  mmol/l (A); either a random or a fasting blood glucose level  $\geq 7.0$  mmol/l (B). An additional outcome measure was the proportion of the population with at least one blood glucose measurement in the record.

### Results

The number (percentage) identified in category A was 3758 (0.10% of the total population); the number in category B was 32 785 (0.90%). Projected to a practice of 7000 patients, around eight patients have biochemical evidence of undiagnosed diabetes, and 68 have results suggesting the need for further follow-up. One-third of people aged over 40 years without diabetes have a blood glucose measurement in the past 2 years in their record.

### Conclusion

People with possible undiagnosed diabetes are readily identifiable in UK primary care databases through electronic searches using blood glucose data. People with borderline levels, who may benefit from interventions to reduce their risk of progression to diabetes, can also be identified using practice-based software.

### Keywords

blood; clinical informatics; diabetes; diagnosis; glucose; screening.

## INTRODUCTION

The global rise in diabetes prevalence poses major challenges for healthcare providers.<sup>1</sup> Symptoms of type 2 diabetes develop insidiously, so that a significant proportion of patients are undiagnosed, even in countries with a well-developed healthcare infrastructure. Up to 1% of the population of England is thought to have undiagnosed or unrecorded diabetes,<sup>2</sup> and is not receiving access to well-organised systematic care and follow-up.<sup>3</sup> In addition, people with impaired glucose regulation are likely to be excluded from the structured follow-up offered to those with diabetes,<sup>4</sup> even though they benefit from interventions to reduce the risk of progression to diabetes,<sup>5-7</sup> and to control cardiovascular risk. Therefore, there is a good case for identifying individuals with evidence of undiagnosed diabetes or impaired glucose regulation.

General practice records might assist in the identification of individuals most likely to have undiagnosed diabetes, but this approach depends largely on the availability of relevant, coded data. In a recent study in the Netherlands, hypertension, cardiovascular disease, and lipid metabolism disorders were identified as the most useful risk factors available in the electronic records.<sup>8</sup> Family history is an important factor but was not coded

*TA Holt, MRCP, FRCGP, clinical lecturer, Health Sciences Research Institute, University of Warwick, Coventry.*

*D Stables, MB ChB, medical director; S O'Hanlon, MA, MRCP, MRCGP, clinical design director, EMIS, Fulford Grange, Leeds. J Hippisley-Cox, PhD, professor of clinical epidemiology and general practice, Centre for Population Studies, Division of Primary Care, University of Nottingham. A Majeed, PhD, professor of primary care, Department of Primary Care and Social Medicine, Imperial College, London.*

### Address for correspondence

Dr Tim A Holt, Health Sciences Research Institute, University of Warwick, Gibbet Hill Road, Coventry CV4 7AL, UK. E-mail: tim.holt@warwick.ac.uk

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consistently and so could not be included. In a community-based study in New Zealand, randomly selected householders were invited for casual blood glucose testing and risk assessment, followed by oral glucose tolerance testing in selected cases.<sup>9</sup> The results suggested that glucose measurements themselves are superior to traditional risk factors alone as a means of identifying groups for formal diabetes screening, particularly in Europeans. A general practice-based targeting strategy based on this principle but utilising existing blood glucose data would depend on their availability in electronic records, and this has not previously been measured in current UK practice. The volume of such data is set to rise following the guidelines of the Joint British Societies, which recommend opportunistic blood glucose measurement in everyone over 40 years undergoing cardiovascular risk assessment.<sup>10</sup>

This study was undertaken to estimate the number of people in the UK with biochemical evidence of undiagnosed diabetes, and the number justifying retesting to clarify their diabetes status, identifiable by existing electronic blood glucose data in primary care. The study was designed to test the utility of electronic searches as a means of targeting this group, and to measure the availability of blood glucose data to support them. This approach has the advantage that the existence of raised blood glucose measurements in a patient's record provides justification for further testing that is independent of the argument for or against population screening for diabetes.

## METHOD

### Study design

A population-based, cross-sectional survey using version 11 of the UK QRESEARCH database was undertaken.<sup>11</sup> This database contains the anonymised electronic healthcare records of over 9 million patients ever registered with 499 general practices throughout the UK. The information recorded on the database includes patient demographics (year of birth, sex, socioeconomic data derived from the UK 2001 census), characteristics (height, weight, smoking status), symptoms (if coded electronically), clinical diagnoses, consultations, referrals, prescribed medication, and results of investigations. Biochemistry results (including electronically-coded blood glucose values) are available that are now transmitted directly into the patients' notes from the local laboratory. The database has been validated by comparing birth and death rates, consultation rates, and prevalence and mortality rates with other data sources including the General Household Survey<sup>12</sup> and the General Practice Research Database.<sup>13</sup> Practices were included in the analysis if they had complete data transmission until at least 1 June 2006.

## How this fits in

The availability of blood glucose data in UK general practice records offers a new opportunity for identifying individuals requiring testing for diabetes. Most practices have patients with biochemical evidence of undiagnosed diabetes, who are identifiable by simple computer searches. As part of practice-based software, these searches may allow such individuals to be identified and followed up during routine care.

Patients were included if they were registered with the practice on 1 June 2006.

### Diagnostic definitions

The current diagnostic criteria for diabetes of the World Health Organization (WHO) were used in this study.<sup>14</sup> A fasting plasma glucose level  $\geq 7.0$  mmol/l on two occasions is diagnostic of diabetes in a patient with no symptoms. In a clearly symptomatic patient, a single raised random plasma glucose level of  $\geq 11.1$  mmol/l can be used to make the diagnosis.

### Patient subsets and code groups

The following subsets of patients were identified according to information in their electronic health record (codes available from the authors):

- patients with a computer-recorded diagnosis of diabetes;
- patients with a computer diagnosis of impaired glucose tolerance or impaired fasting glycaemia;
- patients with at least one random glucose measurement or one fasting glucose measurement; and
- patients with computer-recorded evidence of a normal glucose tolerance test.

### Search strategies

Two alternative electronic search strategies were applied, examining the most recent blood glucose measurement available in the record. Both strategies initially identified patients who do not have a diagnosis of diabetes (or impaired glucose tolerance) and have not had a diagnosis of diabetes excluded by a normal glucose tolerance test, or as indicated by the use of an appropriate Read code, as detailed in the Results section.

#### Strategy A

Patients were included in the results if the most recent blood glucose measurement was a fasting level  $\geq 7.0$  mmol/l or a random level of  $\geq 11.1$  mmol/l.

#### Strategy B

Patients were included in the results if the level (fasting or random) of the most recent blood glucose

**Table 1. Percentages of people with diagnosed diabetes and those identified by strategies A and B in the study.**

Sex	Age band, years	Prevalence of diagnosed diabetes per 100	Percentage of study population identified using Strategy A	Percentage of study population identified using Strategy B
Female	<15	0.15	0.00	0.03
	15-24	0.40	0.01	0.17
	25-44	1.01	0.04	0.56
	45-64	4.05	0.11	0.99
	65-74	9.91	0.22	1.84
	≥75	10.39	0.34	3.57
Male	<15	0.15	0.00	0.03
	15-24	0.42	0.01	0.13
	25-44	1.23	0.04	0.36
	45-64	5.85	0.20	1.30
	65-74	13.53	0.34	2.44
	≥75	13.95	0.36	3.45
Total	All ages	3.54	0.10	0.90

**RESULTS**

**Study population and prevalence of diagnosed diabetes**

A total of 480 general practices met the inclusion criteria for the study. There were 3.63 million patients registered, of whom 50.43% were female, and 8.03% were aged 75 years or over.

A total of 128 421 patients were identified with a computer-recorded diagnosis of diabetes, giving an overall prevalence of 3.54%. The median practice prevalence of diabetes is 3.60%. Table 1 shows the age-sex-specific prevalence rates for a diagnosis of diabetes.

**Exclusions from the target population**

Of the 3.51 million people without a computer-recorded diagnosis of diabetes, 0.27% were excluded from the target population because of a diagnosis of impaired glucose tolerance or impaired fasting glycaemia, a code for ‘diabetes resolved’ (for example, after pregnancy), or a code for ‘diabetes excluded’. As shown in Figure 1, there were 3.49 million people in the target population for further analysis.

**Availability of blood glucose data**

Overall, 1.05 million people (30% of the target population) had at least one computer-recorded blood glucose value, with considerable variation between practices. This figure rises to two-thirds of those aged 65 years or older. Some of these measurements were taken over 10 years ago, but in the past 2 years approximately half of all patients aged over 65 years, one-third of those aged over 40 years, and one-fifth of the total population have undergone blood glucose estimation. The proportion of blood glucose measurements that were clearly fasting was 15.9%. In 22.2% they were reported using a random code, but in 62% of measurements it was not clear from the code whether the sample was fasting or random. For all cases that were not clearly reported as fasting, it was assumed that the sample was random, but some of these measurements may have in fact been taken on fasting samples.

**Primary outcomes**

Using strategy A, 3800 patients were identified from the target population whose last glucose measurement was suggestive of diabetes (that is, a random value of ≥11.1 mmol/l or a fasting value ≥7.0 mmol/l).

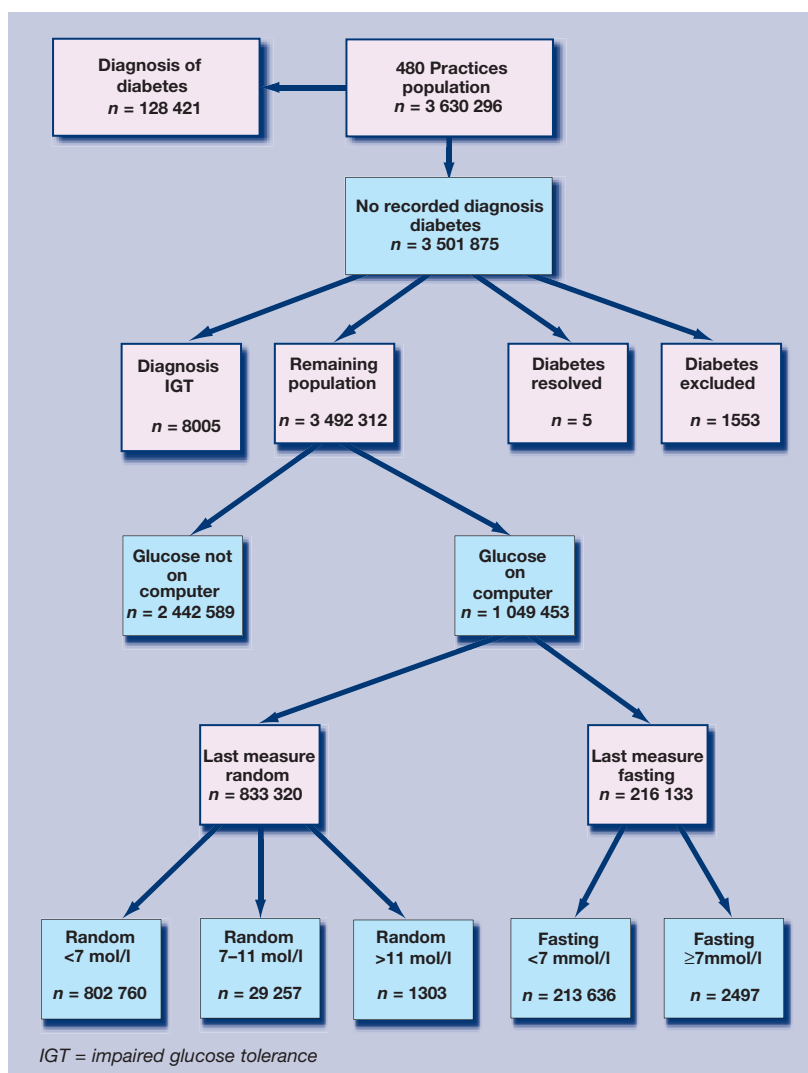
Of those identified, only 1.3% had diabetes excluded on the basis of a subsequent normal oral glucose tolerance test, leaving 3758 patients requiring further investigation or follow-up.

Using strategy B, 33 057 people were identified

**Figure 1. Number and percentage of the study population in each diagnostic category.**

measurement was ≥7.0 mmol/l.

The prevalence of each outcome was also determined by 5-year age-sex band.



where the most recent blood glucose value (random, fasting, or non-specifically coded) was  $\geq 7.0$  mmol/l. This figure fell to 32 785 once those with a normal glucose tolerance test had been excluded. This represents just under 1% of the entire study population and approximately 3.5% of all patients aged over 65 years.

Table 1 shows the age–sex breakdown of patients identified using strategies A and B.

### Time since last recording

Figure 2 shows the time periods since the abnormal glucose measurement according to strategies A and B. In some cases the last recorded value was relatively recent, so the individual may still be in the usual process of follow-up and no other action would be required. The distributions indicate that this was more likely to be the case for strategy A individuals, whose results may be more obviously significant. But in over one-third of the 'A' patients and half of the 'B' patients, the last recorded value was more than 1 year ago. In around one-fifth of the 'A' patients and nearly one-third of the 'B' patients, it was in excess of 2 years.

### Variation between practices

Table 2 shows the mean, median, and interquartile ranges of the numbers identified in the two categories in the 480 practices, demonstrating a wide range of values obtained. The majority of practices (440/480) had at least one strategy A patient identified, and all but one had at least one strategy B patient.

## DISCUSSION

### Summary of main findings

A significant proportion of the population has undergone blood glucose measurement, and the use of simple electronic searches allows us to identify people requiring clarification of their glucose tolerance. The numbers identified varied between practices. The majority (440/480) of practice databases include patients with evidence of undiagnosed diabetes based on the most recent blood glucose measurements (strategy A). Some of these may be known to have diabetes but are not on the practice diabetes register, and are therefore unlikely to receive well-organised, systematic care and follow-up. A proportion of the blood glucose levels reported by laboratories using random or non-specific codes may in fact have been taken from fasting samples.

All but one of the 480 practices in this study's sample included people whose most recent blood glucose level probably requires further follow-up according to current guidelines (strategy B).<sup>10</sup> This would involve a review of symptoms suggestive of

**Table 2. Variation in results among practices.**

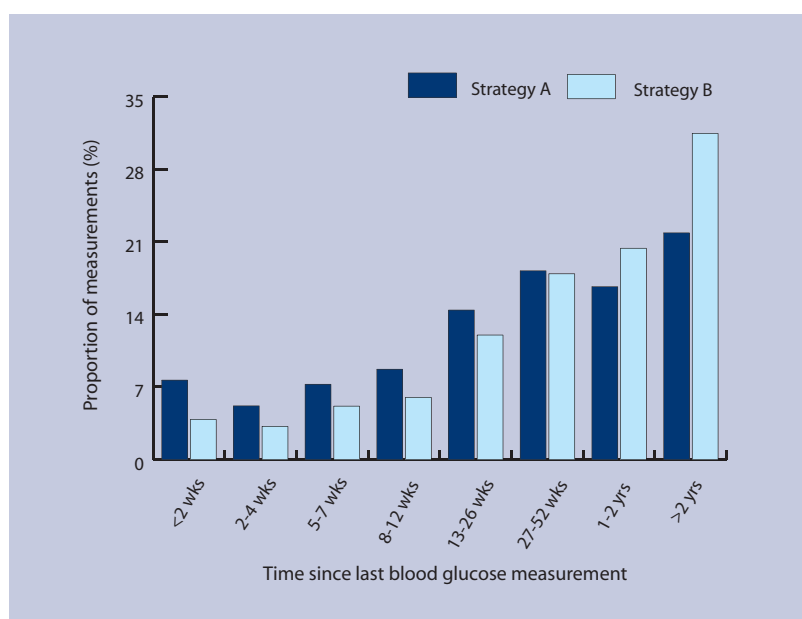
	Strategy A	Strategy B
Mean number of patients per practice	8	68
Median number of patients per practice	5	57
Interquartile range	2–10	30–92
Maximum	67	344
Number of practices (out of 480) with no patients identified	40	1

diabetes, clarification over whether the sample was fasting or random, and/or investigation with a fasting glucose or oral glucose tolerance test.

### Strengths and limitations of the study

This is a large population-based study utilising routinely collected data from general practices all over the UK. The age–sex structure of the study population is similar to national estimates, although the QRESEARCH population is slightly older. The prevalence of diagnosed diabetes in this study (3.54%) is very similar to the national prevalence for all practices in England (QMAS prevalence for 2006 3.60%),<sup>15</sup> suggesting QRESEARCH is likely to be representative of practices for case ascertainment, screening, diagnosis, and electronic recording of diabetes. QRESEARCH uses data exclusively from EMIS (Egton Medical Information Systems) practices. EMIS provides clinical software to approximately 59% of general practices in the UK. The national recommended Read codes used to transmit results to practices from hospital laboratories are the same for EMIS and non-EMIS practices.<sup>16</sup> Through the cross-sectional design of this study it was not possible to determine the

**Figure 2. Proportion of blood glucose measurements identified by strategies A and B according to time interval since the measurement.**



proportion of patients identified who were subsequently diagnosed with diabetes or impaired glucose regulation.

### Comparison with existing literature

This is the first nationwide survey to investigate the potential of practice-based searches for the detection of undiagnosed diabetes. The Diabetes Audit and Research in Tayside Scotland (DARTS) study identified some individuals with isolated hyperglycaemia in healthcare databases who were not on diabetes registers.<sup>17</sup> This study involved just eight general practices, and took place in a small region of Scotland in 1996, when the prevalence of diabetes was significantly lower than today. It predated the introduction of the Quality and Outcomes Framework in 2004 (which promotes the maintenance of electronic diabetes registers),<sup>3</sup> the widespread establishment of laboratory links for electronic data transmission, and the JBS2 report,<sup>10</sup> which established a policy for the follow-up of borderline blood glucose levels and actively encourages the testing of blood glucose in the over-40-year population, through cardiovascular risk assessments.

### Implications for future research and clinical practice

The proportions in these categories in which diabetes or impaired glucose regulation is confirmed on further testing will be investigated by the present authors, using a sample from current primary care, to clarify the usefulness of the software in the identification of undiagnosed diabetes. Further research is also planned to investigate the obstacles to follow-up of borderline blood glucose levels. These might include lack of clarity among practitioners over diagnostic thresholds, failure of laboratories to specify random or fasting results, problems with practice follow-up systems, or lack of patient concordance with invitations for retesting. It can be concluded that there is considerable scope in the UK for using electronic health records to identify people for recall and further assessment, thereby assisting in early detection of diabetes and impaired glucose regulation. Since the completion of this project, EMIS has introduced new software into all its practices for flagging up individuals in the 'A' and 'B' categories, to assist in their identification and follow-up during routine care.

### Ethical approval

QRESEARCH is approved by Trent MREC and all studies are reviewed by the QRESEARCH scientific committee (03/4/021)

### Competing interests

Julia Hippisley-Cox, David Stables and Shaun O'Hanlon are

unpaid directors of QRESEARCH, which is a collaborative venture between the University of Nottingham and EMIS (commercial supplier of computer systems to 59% of general practices in the UK). David Stables and Shaun O'Hanlon both work full-time for EMIS. Publication of this paper could lead to an increased awareness of the scope of the database for research. QRESEARCH undertakes research commissioned by government organisations including the Health and Social Care Information Centre, National Audit Office, Disability Rights Commission, Health Protection Agency, and the Department of Health. There are no other competing interests

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# Detection of undiagnosed diabetes using UK general practice data

TIM A HOLT

## Abstract

**A**n estimated 750,000 people in the UK have diabetes that is either undiagnosed or unrecorded on diabetes registers. Opportunities are missed to prevent or delay complications and reduce cardiovascular risk. This 'missing population' problem has been addressed at various levels: raising awareness among the public; targeted case finding in at-risk groups; and lowering the threshold for investigation of suggestive symptoms among clinicians. Cardiovascular risk assessments are recommended in the UK for the over 40-year-old population and include blood glucose measurements. To further support these measures, this article discusses a recently reported technique for identifying possible cases of undiagnosed diabetes using simple searches on primary care databases, and its implications for practice and future research.

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**Key words:** diabetes, diagnosis, screening, glucose, blood informatics

## Introduction

Patients with diabetes are usually diagnosed several years after the onset of hyperglycaemia<sup>1</sup> and may already have microvascular and macrovascular complications.<sup>2</sup> This adds to epidemiological evidence<sup>3</sup> of a substantial 'missing population', estimated to be 750,000 individuals in the UK.<sup>4</sup> These people are not receiving appropriate care for a potentially disabling condition amenable to preventive measures. Some undiagnosed patients have no symptoms. Intervention in such cases is assumed to be beneficial, but controlled trial evidence of this would be valuable and such a trial is underway.<sup>5</sup> Other undiagnosed patients do have low grade symptoms likely to respond to treatment, and this further supports the case for early detection.

## Early detection strategies

Numerous approaches have been employed to promote early detection. Public awareness raising campaigns include posters to encourage individuals to come forward for testing, based on

Correspondence to: Dr Tim A Holt  
Health Sciences Research Institute, University of Warwick, Gibbet Hill Rd,  
Coventry CV4 7AL, UK.  
Tel: +44 2476 574898; Fax: +44 2476 528375;  
Email: tim.holt@warwick.ac.uk



Tim A Holt

## Abbreviations and acronyms

CVD	cardiovascular disease
EMIS	Egton Medical Information Systems

classical risk factors such as ethnicity, family history, and central obesity. Case finding in primary care has broadened this risk profile to include other factors including anti-hypertensive medication.<sup>6</sup> Such strategies are limited not only by the lack of specificity of some of these predictors, but also by the availability of the necessary data in general practice computer systems.<sup>7</sup>

The Joint British Societies' Guidelines on the Prevention of Cardiovascular Disease in Clinical Practice 2 (JBS2) report of 2005<sup>8</sup> recommended random blood glucose measurement as part of cardiovascular risk assessments in the over 40-year-old population. This is preferable to diabetes screening alone, due to the overlap between diabetes and CVD. The report suggested that random levels of 6.1 mmol/L or above should be followed up with a fasting plasma glucose measurement, and if necessary by a further fasting test or oral glucose tolerance test until the glucose tolerance status is clarified.

## The e-Nudge trial

The 'e-Nudge' is a software tool developed in collaboration between the University of Warwick and the clinical software company EMIS.

It interrogates primary care data to identify patients at risk of CVD and is currently under trial in 19 general practices in Coventry and Warwickshire. The trial protocol<sup>9</sup> describes six categories of patients identified on the basis of estimated cardiovascular risk and on the completeness of recorded risk factor data. Identified patients are flagged up through screen alert messages and regularly updated lists. One of the groups initially included people with possible undiagnosed diabetes based on raised blood glucose values (any level  $\geq 11.1$  mmol/L with no subsequent normal fasting level  $< 7.0$  mmol/L or normal oral glucose tolerance test) and absence from the practice diabetes register. Following installation of the software, the number of patients in each group was measured before the software began operating on a random half of the over 50-year-old population. The baseline data have been published for the groups identified as at raised estimated risk of CVD ( $\geq 20\%$  over 10 years), those with possibly raised risk but incomplete information, and those with known CVD but uncontrolled blood pressure or serum cholesterol.<sup>10</sup> The group involving possible undiagnosed diabetes identified 33 individuals from a denominator population of 36,546 (0.09%). Whilst this figure is small at the practice level, it amounts to significant numbers in larger populations, and creates an opportunity to introduce a new means of identifying undiagnosed cases.

### The QRESEARCH survey

It was unclear whether this issue was a regional one (in Coventry and Warwickshire) or typical of practices all over the UK. It was also unknown from the e-Nudge data how recently the blood glucose measurements were taken. Patients identified would include those whose raised level had been measured the week before with follow-up arranged in the near future, a situation requiring no additional intervention. To answer these questions a new team applied to Nottingham University's QRESEARCH database (a large database derived from the anonymised health records of over 9,000,000

patients) to run a similar (but modified) search on a much larger sample of EMIS practices across the UK. This survey was published earlier in 2008,<sup>11</sup> and involved 480 practices providing more than 3,600,000 electronic records. Two search strategies were applied to the population (of all ages) not on the diabetes register and with no recent 'normal glucose tolerance test' code. The searches examined all blood glucose measurements. These are generally taken on plasma samples and the results transmitted electronically to the practices from the hospital laboratory. Strategy A identified those whose most recent value was in the diagnostic range for diabetes ( $\geq 7.0$  mmol/L fasting or  $\geq 11.1$  mmol/L random plasma glucose, or non-specifically coded). Strategy B identified those whose most recent glucose value (using any code) was 7.0 mmol/L or higher. For strategy A, a similar proportion to the e-Nudge result (0.1%) was found, and for the more inclusive strategy B, 0.9% of the population was identified.<sup>11</sup>

This survey suggested that patients with possible undiagnosed diabetes are identifiable in the majority of UK practices using very simple search strategies on existing data. Of the 480 practices sampled, 440 contained at least one strategy A patient, and all but one contained at least one strategy B patient. The survey also demonstrated that blood glucose has been measured during the previous two years in a third of people over 40 years old without a diagnosis of diabetes. Finally, the results confirmed that the patients identified were not simply those with very recent tests still in the process of active follow-up. In fact, a significant proportion of patients (even in strategy A) had undergone the blood glucose test that identified them more than a year ago.

### Discussion

#### Extrapolating results to UK population

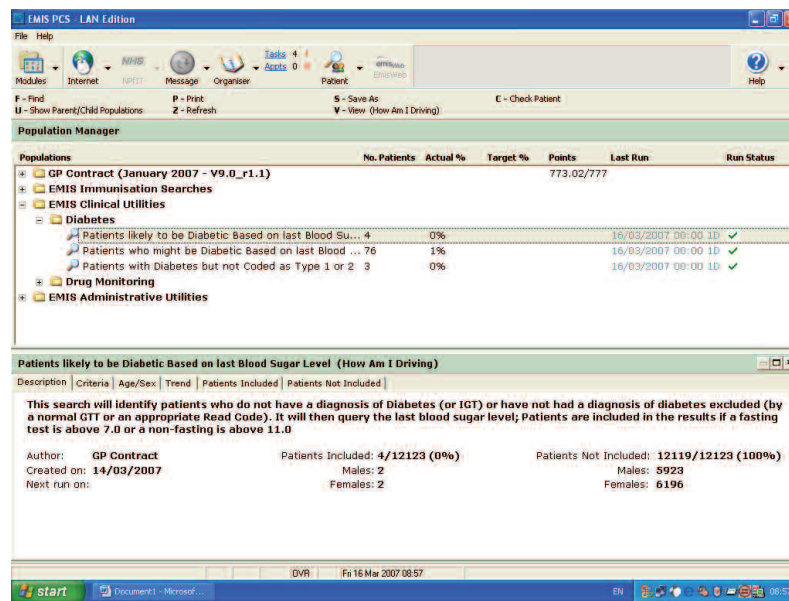
The QRESEARCH database has been validated against other epidemiological data sources and broadly represents the UK public registered with general practice. Data on blood glucose measure-

**Table 1.** Estimation of patients in UK to be identified using strategy A and B (based on Office of National Statistics mid year population estimates for 2004)

Gender	Age band	Estimated UK population	Estimated numbers in UK using strategy A	Estimated numbers in UK using strategy B
Female	< 15 years	5,297,200	218	1,653
Female	15–24 years	3,787,000	425	6,580
Female	25–44 years	8,622,600	3,662	48,694
Female	45–64 years	7,368,000	8,434	73,112
Female	65–74 years	2,658,900	5,834	49,014
Female	> 75 years	2,829,900	9,579	100,920
Male	< 15 years	5,569,500	201	1,862
Male	15–24 years	3,933,300	421	5,307
Male	25–44 years	8,506,800	3,611	30,448
Male	45–64 years	7,170,400	13,982	92,992
Male	65–74 years	2,374,400	8,036	57,987
Male	> 75 years	1,716,700	6,112	59,268
<b>Total</b>		<b>59,835,000</b>	<b>60,516</b>	<b>527,838</b>



**Figure 1.** Screenshot of the EMIS system displaying strategy A individuals. The 'Patients Included' tab produces a drop down list of patient names that can then be right-clicked to browse the medical record directly



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ments are transmitted to EMIS practices in the same way as for other software systems, using electronic links to local hospital laboratories and recognised data transfer protocols. This suggests that the findings are typical of practices throughout the UK and that the results can be extrapolated to the UK population based on the proportion of people in the respective age bands (table 1). This indicates that in the UK there are 60,000 people with probable undiagnosed diabetes who are readily identifiable based on information already within their general practice records.

It also appears that 528,000 people are identifiable who require follow-up of a blood glucose reading. In these cases the likely outcome is less clear, but almost all would justify further testing according to the JBS2 recommendations.<sup>8</sup> Such patients may turn out to have undiagnosed diabetes (particularly if the initial result that identified them was obtained on a fasting sample), or may have impaired glucose regulation, a modifiable risk factor both for future incident diabetes and for CVD.

For either strategy, a proportion may be found to have normal glucose tolerance. Nevertheless, given the existence of a raised blood glucose level ( $\geq 7.0$  mmol/L) at the most recent measurement in their records, it could be argued on both ethical and pragmatic grounds that these groups are a good starting point in the quest for the missing population.

### Implications for practice

At the outset of the QRESEARCH survey, EMIS committed to address the issue through changes to their software system if significant numbers were uncovered, as the QRESEARCH data are

all anonymous and the patients detected cannot be identified individually. Soon after the initial data extraction, when the results indicated high patient numbers, a new software module was developed and installed in all EMIS practices nationally. In a similar way to the e-Nudge, this module creates lists, updated every 24 hours, of identified 'A' and 'B' patients that can be accessed by primary care teams (figure 1). If a patient currently on one of the lists presents to the practice and the electronic record is opened, a screen alert message appears stating, 'Rule out Diabetes – Latest Glucose High' (figure 2).

Meanwhile, the e-Nudge trial continues but with the undiagnosed diabetes group removed, due to the availability of this software module, which is now part of routine care in nearly 60% of UK practices.

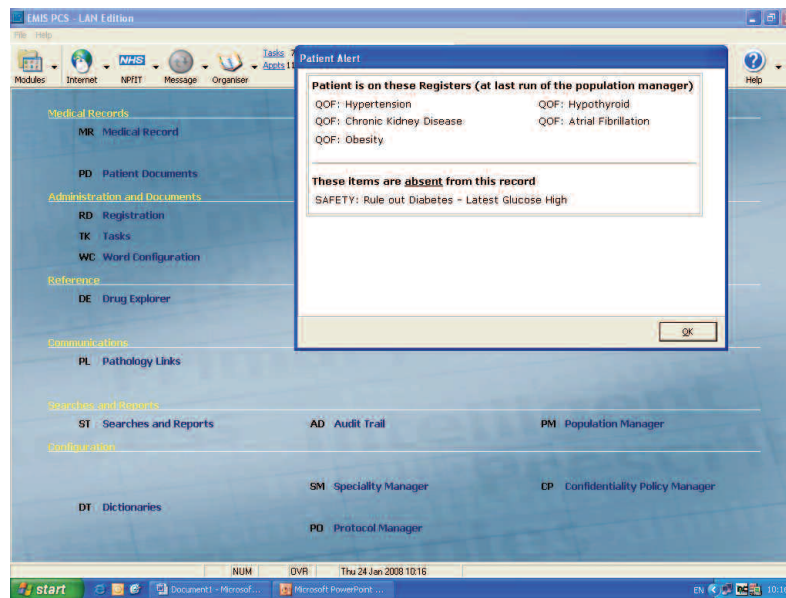
### Implications for other software providers

The EMIS module is based on the same search strategy as that described in the study report,<sup>11</sup> allowing other software providers both in the UK or abroad to develop similar techniques. All that is required is an electronic diabetes register and plasma glucose data searchable in the individual patients' records.

### Further research

The availability of blood glucose data identified in the QRESEARCH project creates an opportunity for including this as a predictor in a new algorithm for assessing diabetes risk. This could usefully support the more traditional risk factors as a means of targeted case finding to identify the missing population

**Figure 2.** Screen alert message appearing on opening the notes of a patient identified at risk of undiagnosed diabetes



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### Key messages

- Patients with probable undiagnosed diabetes are readily identifiable using simple computer searches in general practice
- Others are identifiable who justify follow-up of borderline blood glucose levels
- New software installed into the majority of UK practices flags up these groups as part of routine care
- This supports existing initiatives for identifying the 'missing population' with diabetes

with undiagnosed diabetes and to promote cardiovascular disease prevention. The model of data interrogation on cardiovascular and diabetes risk factor data fed back to clinicians during routine care lends itself to adaptation to emerging risk patterns in the evolving software environment of primary care.

### Acknowledgements

I thank the practices participating in the e-Nudge trial for their collaboration. Thanks also to colleagues on the e-Nudge research team (Margaret Thorogood, Frances Griffiths, Steven Munday and David Stables) and the QRESEARCH project team (Julia Hippisley-Cox, David Stables, Shaun O'Hanlon and Azeem Majeed).

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## 10-MINUTE CONSULTATION

# Raised blood glucose concentration

Tim A Holt,<sup>1</sup> Claire J Holt<sup>2</sup>

<sup>1</sup>Health Sciences Research Institute, University of Warwick, Coventry CV4 7AL

<sup>2</sup>Kenyon Medical Centres, Willenhall, Coventry CV3 3AD

Correspondence to: T Holt  
tim.holt@warwick.ac.uk

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A 56 year old woman recently requested a cholesterol measurement and has come to discuss the results, which include a plasma glucose concentration of 8.3 mmol/l.

### What issues you should cover

- Can diabetes be diagnosed in this patient? Which further tests and what follow-up are needed?
- Was it a fasting or a random sample? If fasting, can the patient confirm she had fasted for at least eight hours?
- Does she have symptoms of diabetes? Some patients asking for a screening test may be concerned about symptoms, perhaps non-specific ones, including those of diabetes (thirst, polyuria, unexplained weight loss).
- Does she have risk factors for diabetes? Discussion might include family history, ethnicity, and history of gestational diabetes or impaired glucose tolerance. Comorbid conditions that raise the risk of diabetes include dyslipidaemia, hypertension, central obesity, and cardiovascular disease.

### What you should do

- If you know that the sample was a fasting one, and the patient gives a clear description of

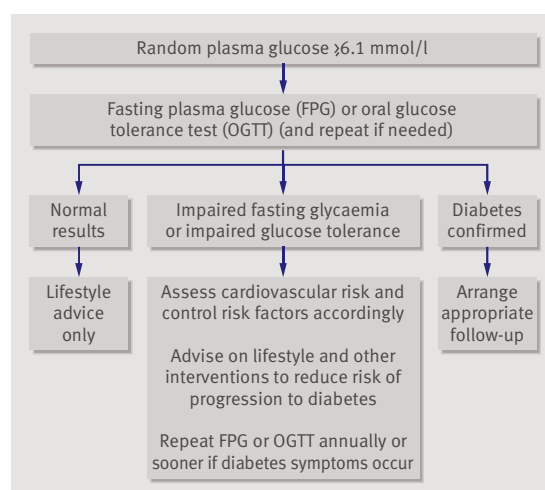
typical symptoms, then you can diagnose diabetes on the basis of this result alone.

Otherwise a further fasting plasma glucose (FPG) or oral glucose tolerance test (OGTT) should be arranged to confirm the diagnosis; this is usually advisable unless the symptoms are convincing. If the patient is of south Asian origin, OGTT is appropriate, as using FPG alone in this group can miss diabetes.

- If it was a random sample, arrange a fasting test. In the context of cardiovascular risk assessment, all concentrations  $\geq 6.1$  mmol/l from a random sample should be followed up in this way. If the fasting sample result is  $< 6.1$  mmol/l then the asymptomatic patient could simply be given lifestyle advice, particularly if the risk of diabetes is low. If the sample suggests impaired fasting glycaemia then follow up with a further fasting sample or OGTT. OGTT is better if there are risk factors or a raised clinical suspicion of diabetes.
- In either case withhold advice on dietary modification until the follow-up fasting test or OGTT, to avoid masking the diagnosis. Clearly agree the follow-up arrangements to discuss the results and give advice, as borderline glucose test results can easily go unnoticed.

### Key messages

- Never pass off a concentration of  $\geq 6.1$  mmol/l in a random glucose test as "normal," particularly in patients aged  $> 40$  years. Further testing is needed to clarify their diabetes status.
- Unless a patient has symptoms that are clearly attributable to diabetes, confirm the diagnosis by a second diagnostic measurement of glucose concentration on a different day.
- Never diagnose impaired glucose tolerance on the basis of a random glucose test. Such patients may have undiagnosed diabetes.
- Fasting plasma glucose measurement may be normal in a patient with diabetes or IGT, and OGTT is more appropriate for some patients with a raised background risk or clinical suspicion.
- Assess cardiovascular risk in patients with impaired glucose regulation (IFG or IGT), recognising the additional influence of this factor, and offer lifestyle advice to reduce the risk of progression to diabetes. Glucose testing should be repeated annually once diabetes has been excluded.



**Follow-up after a random plasma glucose concentration of  $\geq 6.1$  mmol/l. Decisions over choice of test (FPG or OGTT) and the need for repeat testing should be influenced by the perceived risk of diabetes and the presence or absence of diabetes symptoms**

This is part of a series of occasional articles on common problems in primary care. The *BMJ* welcomes contributions from GPs

**Diagnostic thresholds\* (mmol/l) for diabetes, impaired fasting glycaemia (IFG), and impaired glucose tolerance (IGT)**

	Random plasma glucose	Fasting plasma glucose	2 hour post-glucose challenge during OGTT
IFG	NA	6.1-6.9	<7.8
IGT	NA	<7.0	≥7.8 and <11.1
Diabetes	≥11.1	≥7.0	≥11.1

\* From World Health Organization (see Useful reading). Confirm a diagnosis of diabetes by a second diagnostic measurement on a different day if the patient has no symptoms of diabetes. OGTT = oral glucose tolerance test; NA = not applicable.

- “Impaired glucose regulation” covers impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG). IGT can be identified only under standardised conditions of carbohydrate challenge and not from random samples. Both IGT and IFG are risk factors for diabetes, but IGT carries greater cardiovascular risk. The implications for care under current UK policy are the same for either condition: assessment and reduction of overall cardiovascular risk (recognising the 1.5 times greater risk in those with IGT) and annual blood glucose testing (FPG or OGTT) to identify the development of diabetes. A range of interventions may reduce progression to diabetes. Lifestyle interventions seem at least as effective as drugs, whose exact role is still unclear. Targeting of such patients for risk factor control has great potential for prevention of cardiovascular disease.

**Useful reading**

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- Choosing FPG over OGTT is pragmatic and risks missing diabetes or IGT. In choosing tests and planning follow-up, you should consider the patient's risk of developing diabetes and be confident that you have excluded diabetes.

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**Provenance and peer review:** Not commissioned; externally peer reviewed.

**A memorable consultation**

I always wanted to be a surgeon. I was once told that I didn't have the “right personality” to succeed. I didn't listen. Maybe I should have, maybe it was correct. For a start I'm female, and I would be the first to admit that I don't have the “stereotypical surgical personality” ... or so I thought.

Recently, I had one of those rare days that provoke serious thought and personal reflection. My consultant was on holiday, and so I was seeing the patients in the cancer clinic. The last patient arrived with her family. I had been expecting her to attend, and I knew her well. She had presented recently as an emergency while I was on-call. She had been found to have an unusual malignancy, and she was now attending for the results of the investigations and a discussion about management options. The clinic was running late, and I apologised to the patient and her relatives. I introduced myself to her relatives, and they introduced themselves to me. It soon became apparent that her son-in-law was a doctor. He and his wife had travelled a considerable distance to attend the appointment, and they had been expecting to see the consultant. The consultation didn't start well.

Unfortunately, there was bad news to break, and further investigations needed to be arranged before a decision could be made about the operability of the tumour. There was a lot of uncertainty. The son-in-law asked to speak with

me privately afterwards, and the patient gave her consent for this. He thanked me for the explanation and asked me a few more medical questions. He understood. He was very nice. He was very calm. He made a joke. We both laughed. He thanked me again.

I have been thinking about the consultation a lot since. It made a big impression on me, and I have been asking myself why. I think I now know: it made me reflect on myself and see myself in a new light. The consultation made me question how I would have reacted if I had been the relative. I would have been angry, I know that. I would have been impatient. I would have wanted to see the consultant. I would not have been calm.

So maybe I was wrong about myself. Maybe I do have the stereotypical surgical personality after all. This has troubled me. But now, after thinking some more, it's all become clear. The very fact that I have been reflecting on this probably means that I don't have a stereotypical surgical personality after all.

**Sarah Farmer** specialist registrar in otolaryngology, Glan Clwyd Hospital, Rhyl  
sejfarmer@aol.com

Patient consent obtained.  
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