Study Title: SEARCH trial legacy study: long-term follow-up of participants using electronic health records

Short title: SEARCH Trial Legacy Study

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1. SYNOPSIS

Study Title	SEARCH trials legacy study: long-term follow-up of participants with electronic health records	
Internal ref. no. / short title	SEARCH Trial Legacy Study	
Study Design	Extended follow up of randomised controlled trial using electronic health records and other routinely collected data.	
Study Participants	UK participants in SEARCH trial	
Planned Sample Size	SEARCH UK=12,064	
Planned period of research	Planned analyses based on at least 20 years' follow-up from trial initiation (1998) with continued data linkage to allow for future analyses.	
	Objectives	**Outcome Measures**
1	To determine whether participants randomly allocated to treatments leading to lower levels of LDL cholesterol during the scheduled treatment period have a lower risk of dementia	Dementia measured in trial records, hospital episode, death and other health records up to data linkage date
2	To determine whether participants randomly allocated to treatments leading to lower levels of LDL cholesterol during the scheduled treatment period have a lower long-term risk of major vascular and other diseases.	Vascular diseases measured in trial records, hospital episode, death and other health records up to data linkage date
3	To measure the association between baseline and in-trial vascular risk measures with future dementia	Dementia measured in trial records, hospital episode, death and other health records up to data linkage date
4	To measure the association between baseline genetic and blood biomarkers and the occurrence of later disease	Vascular diseases, dementia, neurological disease and other outcomes

2. ABBREVIATIONS

AHA	American Heart Association
ASCEND	A Study of Cardiovascular Events iN Diabetes
ASCOT	The Anglo-Scandinavian Cardiovascular Outcomes Trial
BHF	British Heart Foundation
CRUK	Cancer Research UK
CTSU	Clinical Trial Service Unit
EHR	Electronic health record
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	US Food and Drug Administration
HBS HSC	Honest Broker Service (HBS) for Health and Social Care (HSC)
HES	Hospital Episode Statistics
HDL	High-density lipoprotein
HR	Hazard ratio
HPS2	Heart Protection Study 2
HRA	Health Research Authority
ICF	Informed Consent Form
ISD	Information Services Division Scotland
K-M	Kaplan Meier
MI	myocardial infarction
MRC	Medical Research Council
NDPH	Nuffield Department of Population Health, University of Oxford
NIH	National Institutes of Health
ONS	Office for National Statistics
PPI	Patient and Public Involvement
PPV	Positive Predictive Value
R&D	NHS Trust Research & Development Department
REC	Research Ethics Committee
RR	Risk ratio
SEARCH	Study of the Effectiveness of Additional Reduction in Cholesterol and Homocysteine
UKPDS	United Kingdom Prospective Diabetes Study

3. BACKGROUND AND RATIONALE

3.1. SEARCH

SEARCH was a randomised, multi-centre, factorial trial of LDL cholesterol lowering comparing higher versus standard dose simvastatin, and homocysteine lowering comparing folic acid and vitamin B_{12} supplementation versus placebo in 12,064 patients with a history of myocardial infarction (MI).[1] It was run in 88 UK clinical centres for ten years from 1998 to 2008. This study, in combination with other available data, showed that additional LDL lowering with a high dose statin further reduced major vascular events,[1–3] but that folic acid and vitamin B12 supplementation did not have beneficial effects on vascular outcomes.[4]

In the vitamin comparison, during a median 6.7 years of follow-up, major vascular events occurred in 1537 of 6033 participants (25.5%) allocated folic acid plus vitamin B12 vs 1493 of 6031 participants (24.8%) allocated placebo (risk ratio [RR], 1.04; 95% confidence interval [CI], 0.97-1.12; P=0.28), with no demonstrable effect on fatal or nonfatal ischaemic or haemorrhagic stroke (269 vs 265, RR 1.02; 95% CI: 0.86-1.21).

In the simvastatin comparison, major vascular events occurred during the scheduled treatment period in 1477 (24.5%) of the 6031 participants allocated 80 mg simvastatin versus 1553 (25·7%) of the 6033 allocated 20 mg simvastatin (RR 0·94, 95% CI: 0.88–1.01; p=0.10) with no significant effect on fatal or non-fatal ischaemic or haemorrhagic stroke (255 vs 279, RR 0.91, 95% CI: 0.77-1.08), p=0.3).

3.2. CHOLESTEROL LEVELS AND DEMENTIA

Cholesterol levels are of particular interest because a genetic risk factor for Alzheimer's disease is the ε4 allele of the ApoE gene. This allele codes for the E4 isoform of a lipid chaperone which is found in intermediate density lipoprotein and chylomicrons. It binds to receptors in low-density lipoprotein and other lipid transport species, and is involved in the neuronal transport of cholesterol. People with an ε4 allele have higher levels of total cholesterol (about 0.25-0.5 mmol/L higher) and triglycerides than those without, and therefore higher blood LDL cholesterol is one potential mechanism for the effect of the ε4 allele.[5] In the brain, the role of ApoE is less certain, but it is clearly a strong risk marker for dementia.

In observational studies, higher midlife total cholesterol is associated with later life cognitive impairment or dementia[6–8] though the magnitude of this effect, the associations with lipid sub-fractions, or the extent to which this is mediated by confounding by other vascular risk factors is unclear. Two meta-analyses that mixed observational studies with randomized trials suggested statins reduce the risk of dementia by about a third (OR 0.70: 95% CI 0.59- 0.83),[9,10] although there was no evidence of reduction in cognitive impairment at the end of the scheduled treatment period in the large randomised trials.[11]

Nor did either of the randomised trials that measured short term (<5 years) cognitive performance as a pre-specified outcome show any reduction in the rate of deterioration of cognitive abilities or end of trial cognitive ability with pravastatin[12] or simvastatin.[13] There does not seem to be any effect of statins on the rate of deterioration of dementia once it has developed, although the trials have all been small (<1000).[14,15] A recent Mendelian randomisation study of 3,904 patients with late onset Alzheimer's disease, and 6,664 controls did not show any change in risk of dementia in those with higher predicted lifetime levels of LDL, HDL or triglyceride lipid fractions, though the genetic risk score only explained a small proportion of the variance of lipid levels, and so the study may have been underpowered.[16]

In 2012, the FDA added a warning to the statin product label stating that some patients may experience "ill-defined memory loss" and "confusion." This warning was based mainly on small randomised trials and observational data, including case reports. The AHA/American Stroke Association clinical guidelines recommend:

"in people at risk for vascular cognitive impairment, treatment of hypercholesterolemia may be reasonable (Class IIb; Level of Evidence B)."[17]

Therefore, there is uncertainty about the long-term effects of LDL-cholesterol lowering with statins or other agents on the risk of dementia.

3.3. VASCULAR RISK AND DEMENTIA

Dementia is a condition that develops over a long period before manifesting in a clinical diagnosis. In the short-term (up to 10 years) lower cardiovascular risk factor levels have often been associated with an increased risk of dementia, which may be because of reverse causal effects of the incipient dementia leading to lower levels. However, raised mid-life levels of cardiovascular risk factors (such as LDL-cholesterol) have been found to be associated with increased risk of dementia 15-20 years later. There is little data, however, on whether raised levels of cardiovascular risk factors at older ages are associated with an increased risk of dementia 15-20 years later. Continued follow-up for dementia in studies in older people initiated many years ago is therefore extremely valuable for investigating such effects now (rather than having to wait much longer for more recent studies like UK Biobank to acquire long follow-up). Our series of large-scale cardiovascular trials from The Heart Protection Study[13] (HPS) through to the recently completed ASCEND[18] trial have recruited over 60,000 UK participants at high vascular disease risk and with a mean age of about 62 at recruitment.

Dementia is a leading cause of death in the UK and it is likely that over a third of these populations will develop dementia at some point. Hence, many people in these older studies may by now have developed dementia. Therefore, these studies now constitute a uniquely rich resource for study of the relationships of vascular risk factors to dementia incidence many years later. Separately, HES data in HPS and ASCEND studies is being acquired but larger numbers are needed. This study will look at the association of vascular risk factors measured at baseline with dementia incidence

at various times into the future, with longer delays between measurement of risk factors at recruitment and incidence of dementia being particularly valuable.

3.4. LEGACY EFFECTS OF LDL-CHOLESTEROL LOWERING

There may be important post-trial 'legacy' effects after a period of treatment with LDL-cholesterol lowering agents. LDL cholesterol lowering with a statin might have important effects on the future clinical course of atherosclerosis. Twenty year follow up of the WOSCOPS study demonstrated a reduction in all-cause mortality (HR 0.87; 95% CI: 0.69-0.90), mainly attributable to cardiovascular deaths in the pravastatin arm. There were reductions in hospitalisations for myocardial infarction (24%) and heart failure (35%), although not due to non-cardiovascular causes.[19] In the ASCOT trial long-term follow-up (median 15 years), there were fewer deaths in participants allocated to atorvastatin than in control (HR 0.85; 95% CI: 0.72–0.99).[20]

Based on these findings, a follow-up study is proposed that will determine how long the "legacy effect" after LDL-cholesterol lowering lasts, and to understand better the effects of early LDL cholesterol lowering in patients with a history of vascular disease on important long-term clinical outcomes.

3.5. GENETIC AND BIOMARKER ANALYSIS OF THE SEARCH COHORT

In order to improve our understanding of vascular disease and its treatments, genomic and other relevant blood-based analytic studies of cardiovascular and other diseases, as well as its risk factors and potential sequela (e.g. cognitive function), and of patient response to therapy will be undertaken. For example, through the use of genome-wide association studies to identify new genetic determinants, Mendelian randomization to explore potentially causal relationships, genetic risk scores to examine potential interactions and genetic correlations, and other genomic and blood-based studies (e.g. methylation) to examine wider features of the genome and their relevance to the prevention of and treatment for vascular disease. As such, the SEARCH trial data provides a unique opportunity to address and answer questions that other smaller, less well phenotyped studies cannot.

Genotyping/sequencing and generation of other measures within the above remit will be undertaken at specialist laboratories under strict contractual agreements (e.g. REGENERON, USA; McGill University, Canada; Leicester, UK). All data will be returned to Oxford for statistical analyses. In addition, pseudo-anonymised genomic, phenotypic and outcome data may be shared with collaborators for specific studies and additional statistical analyses where necessary.

4. STUDY DESIGN

4.1. EXTENDED FOLLOW UP OF A RANDOMISED CONTROLLED TRIAL USING ELECTRONIC health records and within trial data

Record level data will be requested from NHS Digital (or appropriate equivalent, in the case of the devolved administrations) after all necessary approvals have been granted with repeat requests on an on-going basis. The data requested will include, but will not be limited to, Hospital Episode Statistics (HES), mental health data and mortality data and their equivalents in devolved administrations.

5. STUDY OBJECTIVES

1. To determine whether participants randomly allocated to treatments leading to lower levels of LDL cholesterol or lower homocysteine have a lower risk of dementia
2. To determine whether participants randomly allocated to treatments leading to lower levels of LDL cholesterol or lower homocysteine have other long-term health effects
3. To measure the association between baseline and in-trial vascular risk measures with future dementia
4. To determine the association between DNA and plasma markers with dementia and other long-term health effects, particularly lipid fractions and ApoE alleles

6. STUDY POPULATION

All participants in SEARCH where linkage is possible to resources held by NHS Digital and NHS National Services of Scotland, Northern Ireland Statistics Research Agency.

7. INTERVENTION

No interventions are planned as part of this study.

8. OUTCOME ASCERTAINMENT

The following outcomes will be measured in linked electronic health data: dementia, stroke, all major cardiovascular disorders, other vascular disease complications, myopathies, heart failure, renal impairment, other health and care outcomes and death. UK participants will be linked with the following datasets:

1. Hospital episode statistics (HES) (admitted patients care, emergency care, critical care and outpatients), mental health and death statistics in England and Wales held by NHS Digital
2. Scottish Morbidity Record (SMR) and death statistics in Scotland held by Information and Services Division (ISD), of NHS Scotland
3. Hospital activity statistics in Northern Ireland, Honest Broker Service (HBS) for Health and Social Care (HSC), Northern Ireland Statistics and Research Agency (www.hscbusiness.hscni.net).
4. Existing data within SEARCH systems and records.

Events occurring in-trial will be defined as in the original trial procedures. Definitions are:

Stroke

Stroke will be defined as an acute symptomatic episode of focal or global neurological dysfunction caused by brain, spinal or retinal vascular injury as a result of infarction or haemorrhage.

Data sources

EHR/death records

ICD codes will be used to define stroke of different types when recorded in the primary or secondary position (approx. to 94% (95% CIs 88% to 98%) PPV, pers. comm. Kristiina Rannikmae). Date of diagnosis will be recorded. Note: no laterality is likely to be available in these records.

Within trial assessment of stroke

Dementia

Dementia is defined as a chronic or persistent disorder of the mental processes caused by brain disease or injury and marked by memory disorders, behavioural and psychological symptoms with impaired reasoning. For the purposes of analysis, all cause dementia will be used. In secondary analysis, should there be sufficient data, vascular dementia will be looked at, Alzheimer's dementia and other dementias and a broader outcome including all outcomes indicative of cognitive impairment.

Data sources:

EHR/death records.

Mental health records

Within trial measurement of dementia

Myocardial infarction:

HES definition of MI

Data sources:

EHR/death records

Within trial measurement of myocardial infarction

In addition, other codes will be examined indicating major vascular and other diseases, including (not limited to):

- Admissions and deaths due to heart failure
- Surgery on large arteries: aorta, carotid, brachial, femoral, iliac etc.
- Acute coronary syndromes
- Cardiac revascularisation procedures by interventional cardiologists or cardiac surgeons
- Cardiac valve surgery
- Renal replacement therapy
- All mortality

9. DISSENT

Participants who have already opted out from having their data stored by NHS Digital will be excluded. In addition, participants who have read the privacy notice and have decided that they

do not wish their data to be used in this study will be able to opt out. The privacy notice will be placed on the original trial website (http://www.ctsu.ox.ac.uk/~search/), and is a supplement to the NDPH Privacy notice (https://www.ndph.ox.ac.uk/about/data-privacy-notice-1/ndph-privacy-policy-for-research-participants)

10. GENETIC AND PROTEIN BIOMARKER ANALYSES

During the SEARCH study, participants provided blood samples for long-term storage and subsequent analyses. SEARCH has an extensively phenotyped database, and active follow-up during the scheduled treatment period (in particular, for mortality, major vascular events, cancer and other major morbidity.

Genetic, proteomic and metabolomic analyses can provide additional valuable scientific insight into treatment response, the risks and causes of cardiovascular event and other related chronic diseases and potential sequela (e.g. cognitive function) especially when linked to traditional biomarker and extensive phenotypic data and to long-term prospective follow-up information. As such, the SEARCH data provides a unique opportunity to address and answer questions that other smaller, less well phenotyped studies cannot.

Hence, in order to improve understanding of vascular disease and its treatments, genomic and other relevant blood-based analytic studies will be undertaken in stored buffy coat and plasma to ascertain between markers of cardiovascular disease, as well as its risk factors and consequences, and of patient response to therapy.

Genomic and blood-based analyses will address a wide variety of aims in order to generate new biological insights and influence therapeutic developments including:

- Assessing clinical benefit of therapy by strata of genetic risk/polygenic risk scores
- Identifying genetic determinants of treatment efficacy and adverse events as well as wider cardiovascular risk factors and outcomes using hypothesis-free genome-wide association analyses as well as candidate gene approaches
- Determining the causal relevance of risk factors and therapeutic mechanisms for disease as well as the potential effects of treatment using Mendelian randomization analyses
- Elucidating functional mechanisms relevant to the prevention and treatment of cardiovascular disease by exploring rare variation in coding regions using single-variant and gene-burden tests

10.1. METHODS

Genome-wide genotyping will be undertaken using the up-to-date genome arrays, which combines genome-wide content, curated clinical research variants, and quality control markers for precision medicine research. Subsequently, genomic assays will be performed, such as exome sequencing, as appropriate.

Genotyping/sequencing and generation of other genomic and biomarker measures within the above remit will be undertaken at specialist laboratories under strict contractual agreements (e.g. REGENERON, USA; McGill University, Canada; Leicester, UK). All data will be returned to Oxford for statistical analyses. In addition, pseudo-anonymised genomic, phenotypic and outcome data may be shared with collaborators for specific studies and additional statistical analyses where necessary.

Protein analyses will be performed using up-to-date proteomic chips and with individual ELISA tests where these will be expected to provide useful information.

All published research findings will be openly accessible to the public, but there will be no feedback of individual findings to the study participants.

11. STATISTICAL ANALYSES

Analyses of randomised interventions will be by "intention to treat" and results will be displayed using Kaplan-Meier survival analyses. Appropriate survival analysis methods (e.g. Log-rank, Cox-regression analysis) will be used to compare the risk ratios for first occurrence post-randomisation of each outcome of interest (e.g. stroke, myocardial infarction, dementia, mortality) between both allocated treatment groups. The association between baseline vascular risk with later dementia will be assessed.

The first planned analyses will be based on at least 20 years' follow-up from trial initiation with further analyses planned at approximately 5 yearly intervals based on on-going linkage to NHS records.

12. DATA MANAGEMENT

12.1. ACCESS TO DATA

All data will be transferred, handled and processed in agreement with the NHS Digital Data Sharing Framework Contract, and will be subject to Fair Processing requirements.

12.2. DATA RECORDING AND RECORD KEEPING (SEE APPENDIX B FOR DATA FLOW)

NHS Digital and NHS Scotland hold the linkage between trial participant numbers and participant identifiers. This will allow NHS Digital and NHS Scotland to create a dataset of trial participant numbers linked to HES and other records. Data will be received back by Oxford in an encrypted format via an approved transfer method. Each participant will be identified by trial identifier only at this stage, not with name, date of birth etc. HES and other data will be linked with data already held on participants for SEARCH. These linkages will be performed between data received from NHS Digital/ISD with anonymised trial identifiers in the University of Oxford Clinical Trial Service Unit (CTSU), Nuffield Department of Population Health (NDPH).

The data will be stored at the CTSU, Nuffield Department of Population Health (NDPH) Richard Doll Building, University of Oxford. Any CTSU and NDPH researchers involved will have appropriate training in information governance and in handling confidential and participant sensitive data.

The NDPH servers are protected against unauthorised external access by an appropriate strength firewall. Access to patient identifiable information is protected by the appropriate authentication procedures (user IDs and passwords). Authentication is only given to personnel with an approved need, and authorisation, to access the required data. Only personnel involved in the long-term follow-up study for SEARCH (processing and analysing data) will have authorised access to this data. NDPH has a Corporate Level Security Policy that has been fully adopted by management and will apply fully to the long-term follow-up study. The data protection Registration Number is Z575783X.

Anonymised datasets will be kept indefinitely to provide: an audit trail for published findings, ability to respond to regulatory requests for further information and for further analysis.

13. ETHICAL AND REGULATORY CONSIDERATIONS

The protocol, previous informed consent forms and PPI and other supporting materials will be submitted to an appropriate Research Ethics Committee (REC), Confidential Advisory Committee and the HRA for approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

Participants will not be approached for further consent and data sharing agreements will be in place accordingly.

14. FUNDING

Nuffield Department of Population Health, University of Oxford.

15. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge the source of funding for the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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17. APPENDIX A: COMMENTS FROM 6 PPI PANELS

The proposed use of patient identifiable data is to identify participants based on similar methods previously used by the NDPH, University of Oxford group in other large-scale trials. The data to be gained is similar to those required for previous studies, in which more than 230 000 participants were identified (without consent) for recruitment into the study with no significant problems encountered, the ASCOT study in Imperial College, and the ACST-1 study. Six patient and public panels were approached to test the acceptability of follow-up in electronic health records of participants from old randomised controlled trials that were designed before long-term follow up in electronic health records was thought to be routinely feasible. The following panels were consulted:

1. SEARCH and HPS2-THRIVE study participants
2. NIHR Stroke Research Network Panel
3. Clinical Trial Service Unit, University of Oxford
4. University College London PPI group
5. ASCOT participants PPI group
6. OCDEM PPI Group

17.1. STUDY PARTICIPANT FEEDBACK

Participants from the SEARCH main trial and also another large study (HPS-THRIVE) were approached to give feedback on the acceptability of this protocol from a participant perspective:

"As a participant I am perfectly happy for my data to be analysed as described and cannot believe others won't be. So I do not think additional consent is required."

"As a participant in both the SEARCH and HPS2-THRIVE trials I have no problem in giving the OK to this new work."

"I do not see any issue with the approach and procedure being proposed, and agree the process should effectively manage any risk to confidentiality. I am also of the opinion that participants who sign up for trials want their data used for effective on-going research. I would therefore very much support the study."

"However after considering your reasons for using this unique data long-term and the fact that through encryption, privacy will be protected; all overrides my concerns."

17.2. NIHR, CTSU AND UCL GROUPS

The following questions were asked:

Do you think the research proposed here is of sufficient interest and could have sufficient benefits to warrant linking information from GP and hospital records to participants' trial data?

Yes: 33/35 (94%)

No: 0

Unsure 2/35 (6%)

Do you agree that in the circumstances described here it is not practical to seek individual patient consent and therefore it is reasonable to carry out the research in the way described here?

Yes: 27/36 (75%)

No: 3/36 (8%)

Unsure 6/36 (17%)

Do you agree that concerns around individual participant privacy are extremely low?

Yes: 24/35 (69%)

No: 4/34 (12%)

Unsure 6/34 (18%)

Do you have any other concerns about the project that have not been made sufficiently clear?

Yes: 6/36 (17%)

No: 26/36 (72%)

Unsure 4/36 (11%)

17.3. ASCOT TRIAL PARTICIPANTS

Question 1

	Yes	No	Don't know
Do you think that this research study is a good idea?	19/19 (100%)	0	0

Question 2: Why do you think it is a good or bad idea?

All respondents thought the project was a good idea. Some representative comments:

"More research in an ageing population can only be a good thing"

"It makes sense to carry out a study on dementia"

"Any research into the causes of dementia is a good thing. It is a progressive disease which affects many people"

"I think there will be long term benefits as a result of this. Benefits would not otherwise be evident"

"If [dementia] could be avoided, it would be excellent. It would save the NHS money, families distress and enable those with the disease to continue contributing to their communities"

"Any potential resource held in medical records should be used to advance research and knowledge"

"All research helps"

"If it helps someone it has to be good"

"I would be happy if the ASCOT data could be of assistance in pursuing knowledge of dementia"

Question 3

	Yes	No	Don't know
Do you have any concerns about such a study being carried out?	0	19/19 (100%)	0

Conclusion

All respondents felt that the research was a good idea, and none had any concerns about the project. No respondent has concerns about the use of medical records for this research question.

17.4. OCDEM PPI GROUP

	1	2	3	4
Do you think this research study is a good idea?	Yes	Yes	Yes	Yes
If YES, please say why	Any study that can reduce the worst effects of diabetes	It seems sensible to me to that we study if the risk of	It is well known that poorly controlled diabetes increases	If a correlation between long term blood glucose

	should be supported. Any reduction that can be made in the number of diabetic amputations should be actively promoted	complications (for T2D) can be reduced by the use if certain medications and what the benefits might also be.	the chnace of heart disease, strokes, kidney failure etc., so any research that can give possible improvements in treatments / medicines has to be a very good thing	control and dementia, death or other major diseases (e.g. heart attacks, strokes and kidney disease) can be established, then it is potentially worth investing in research to establish the cause(s).
If NO, please say why				
Do you think it is acceptable to look further at the data from participants in UKPDS without asking for consent again?	Yes	Yes	Yes	I don't know
If YES, please say why	**Once one has given permission to take part in a study, it should follow on that continuation studies MUST be included**	Had I signed up for the original study then I would have no objection – so I am carrying that logic forward	Patients have already given you permission to look at their data; exploring that data further is no more intrusive than the first study and will expland knowledge on ho diabetes may lead to dementia or other ocnditions if controlled	It depends on the exact nature of the consent they gave for the UKPDS research. I.e. what did the consent form they signed say? E.g. if the form said that thy would be contacted should further use of their data be a possibility, then it does not seem reasonable to use their data without requesting explicit permission for further use of that data.
If NO, please say why				
Do you have any other comments about this research?	See my initial comments	I would insist that the electronic data interface described is robust and not a laptop on a train …	Given the number of people being diagnosed with diabetes and the huge costs to the NHS any researcg that may lead to improvements in care has to be a good	

			thing. Patients also need to be proactice in their treatment	

18. APPENDIX B: DATA FLOW DIAGRAM