Study Title: UK Prospective Diabetes Study (UKPDS) Legacy Study: long-term follow-up of participants into electronic health records

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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. SYNOPSIS

Study Title	UK Prospective Diabetes Study (UKPDS) Legacy Study: long term follow up of participants into electronic health records	
Internal ref. no. / short title	UKPDS electronic health record follow up	
Study Design	Extended follow up of a randomised control trial into electronic health records and other routinely collected data.	
Study Participants	UK participants in UKPDS trial	
Planned Sample Size	5,102	
Planned period of research	5 years: follow-up data acquired for 40 years post trial initiation (1977 – 2019)	
	Objectives	**Outcome Measures**
1	To determine whether participants randomly allocated to tight, rather than less tight, blood pressure control have a lower risk of dementia	Dementia measured in UKPDS records, hospital episode, death and other health records up to data linkage date (estimated 2019))
2	To determine whether participants randomly allocated to intensive, rather than conventional, glucose control have a lower risk of dementia	Dementia measured in UKPDS records, hospital episode, death and other health records up to data linkage date (estimated 2019)
3	To determine whether tight blood pressure control or intensive glucose control reduce the long-term risk of major vascular diseases in diabetes	Vascular diseases measured in UKPDS records, hospital episode, death and other health records up to data linkage date (estimated 2019)
4	To determine whether tight blood pressure control or intensive glucose control reduces long-term health resource use and total burden of disease in diabetes	Health resources measured in UKPDS records, hospital episode, death and other health records up to data linkage date (estimated 2019)
5	To investigate use of health care resources in secondary care by patients with diabetes	UKPDS records, hospital episode, death and other health records up to data linkage date (estimated 2019)

2. ABBREVIATIONS

BHF	British Heart Foundation
NDPH	Nuffield Department of Population Health, University of Oxford
DUK	Diabetes UK
HERC	Health Economics Research Centre, University of Oxford
HRA	Health Research Authority
ICF	Informed Consent Form
MRC	Medical Research Council
NIH	National Institutes of Health
ONS	Office for National Statistics
PPI	Patient and Public Involvement
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
UKPDS	United Kingdom Prospective Diabetes Study

3. BACKGROUND AND RATIONALE

3.1. The UKPDS

The UKPDS was a randomised, multi-centre trial of glucose-lowering and antihypertensive therapies in 5102 patients with newly diagnosed type 2 diabetes that ran in 23 clinical centres for twenty years from 1977 to 1997[1]. Funded by the MRC, NIH, BHF, DUK and a consortium of pharmaceutical companies, this £25M study showed conclusively that that the life-threatening complications of type 2 diabetes could be reduced by more intensive management with existing treatments.

The study demonstrated that maintaining improved glycaemic control, with sulfonylurea or insulin therapy (median HbA_{1c} 7.0 % *versus* 7.9% over median 10 years), reduced the risk of any diabetes-related endpoint by 12%[2]. The risk of microvascular endpoints was reduced by 25%, the appearance of microalbuminuria by 33% and there was a 16% non-significant reduced risk of myocardial infarction (p=0.052). Fears that sulfonylurea or insulin therapies may be harmful were allayed as no increase was observed with these agents in the incidence of cardiovascular deaths, myocardial infarction or sudden death. Although neither of these therapies impaired quality of life, both increased the risk of hypoglycaemia and of weight gain. In overweight patients allocated to metformin as first line therapy, the risk of any diabetes-related endpoint was reduced by 32%, diabetes-related death by 42% and myocardial infarction by 39% with no weight gain, and little increase in the risk of hypoglycaemia[3]. A health economic analysis showed metformin to be cost effective as well as clinically beneficial[4].

The trial also demonstrated that tight blood pressure control in hypertensive patients with diabetes, with a difference between groups of 10 and 4 mm Hg in systolic and diastolic blood pressure respectively, reduced both microvascular and macrovascular disease[5]. Cost-effectiveness analyses showed that cost savings from the reduction in diabetic complications outweighed the cost of the additional medication required, but not the extra staff costs involved[6,7].

Following closeout of the UKPDS in 1997, a ten-year post-trial monitoring period to 2007 was initiated. Patients returned to community or hospital-based diabetes care according to their clinical needs, with no attempt to maintain previously randomised therapies. In the first five years, patients continued to be seen annually in UKPDS clinics, with continued standardized collection of outcome data. Clinical examinations every three years were also continued. Patients who were unable to attend clinics were sent European Quality of Life-5 Dimensions (EQ-5D) and health resource use questionnaires, and additional questionnaires were sent to their general practitioners to capture possible clinical outcomes. In years six to ten, these questionnaires were used to follow patients remotely, since funding for clinical visits were not available. Final questionnaires were sent to all remaining patients after the cutoff for the censoring of post-trial data on 30th September, 2007. The results of the ten-year post-trial monitoring period were published in 2008, which reported the long-term effects on important diabetes-related clinical

outcomes of early intensive glucose control (Glucose Control Study) and tight blood pressure control (Blood Pressure Control Study) in this cohort[8,9]. In the Glucose Control Study, despite an early loss of glycaemic differences between groups post-trial termination, relative risk reductions persisted at ten years for any diabetes-related endpoint (9%, p=0.04) and microvascular disease (24%, p=0.001), and risk reductions for myocardial infarction (15%, p=0.01) and death from any cause (13%, p-0.007) emerged over time, as more events occurred[8]. In the metformin group, significant risk reductions persisted for any diabetes-related end point (21%, p=0.01), myocardial infarction (33%, p=0.005), and death from any cause (27%, p=0.002)[8]. These persisting therapeutic benefits have been termed a "legacy" effect. In the Blood Pressure Control Study differences in blood pressure between the two groups during the trial disappeared within two years after termination of the trial. Significant relative risk reductions found during the trial for any diabetes-related end point, diabetes-related death, microvascular disease, and stroke in the group receiving tight, as compared to less tight, blood pressure control were not sustained during the ten-year post trial follow-up[9].

3.2. The association between diabetes with cognitive impairment and dementia

Type 2 diabetes is associated with later life cognitive decline[10] and with dementia[11]. The mediators for this association are multi-factorial: they include cerebral small vessel disease, silent and symptomatic brain infarcts and brain atrophy[12]. It is uncertain what property of diabetes leads to the increased risk of dementia: this may be co-morbid hypertension, hypercholesterolemia. The diabetes-related factors that are associated with cognitive decline are less clear, though probably include treatment-related hypoglycaemia, co-morbid hypertension, stroke and hyperglycaemia.

From 1983 to 1989, 1441 patients with type 1 diabetes with a median age of 27 years were enrolled into the Diabetes Control and Complications Trial (DCCT) of intensive versus conventional control of hyperglycaemia. At an average of 18 years after enrolment, when the participants reached a mean age of 46 years, cognition was measured. The intensity of control glucose levels made no statistically significant difference to psychological measures cognition, despite a higher rate of hypoglycaemic episodes in the intensive control group[13]. However, patients were young at final follow up, hence dementia may not have had time to develop.

As part of the ACCORD study, 2977 patients with type 2 diabetes with a mean age of 63 years were randomised to intensive versus conventional glycaemic control. The trial demonstrated higher mortality in the intensive control group and no difference in cardiovascular outcomes between groups. Cognition was measured at 20 and 40 months post enrolment, and in a subgroup, MRI volumes were measured. There was no difference in the 40 month cognitive assessment between the groups, though total brain volume was greater in the intensively controlled group. Early brain volume changes may predict later dementia, and therefore may be an early biomarker of the neuro-protective effect of intensive control of glucose[14].

There is therefore uncertainty about the degree to which better control of glucose in patients with diabetes lowers dementia incidence.

3.3. Blood pressure and dementia

In observational studies, high blood pressure, particularly in mid-life is associated with an increased risk of dementia or cognitive decline (~6.5% greater decline in those with hypertension)[15-17]. The presence of hypertension is associated with a greater risk of vascular dementia (OR 1.59, 95%CI 1.29 – 1.95), with all dementia and with cerebral atrophy and white matter change, the radiological correlates of the pathological changes of vascular dementia and Alzheimer's disease[17-19]. However, these associations are attenuated after adjustment for early life cognitive ability[20], and in meta-analyses of individual patient observational data across multiple studies[21].

Two meta-analyses of trial data examined two different groups of four randomised trials comparing control or placebo with blood pressure lowering in participants without dementia[22,23]. In these studies, lowering blood pressure led to a borderline statistically significant (P=0.045) reduction in the risk of dementia over the period of trial follow up of between -11% (95%CI:-26% to +7%) and 13% (-22% to 0%). Follow up to dementia was short (~5 years), and based on a modest number of participants developing dementia (~1000). In patients with dementia, blood pressure lowering appears to have no effect on the progression of cognitive impairment[24].

Whilst clinical guidelines recommend the treatment of blood pressure to lower the future risk of dementia[25,26], these recommendations are based predominantly on observational data which are subject to biases and unrecognised confounding. Influential reviews have called for individual participant data meta-analyses of the existing trials, and trials of blood pressure lowering with a longer duration to strengthen recommendations to clinicians and patients.

There is therefore uncertainty about the degree to which pharmacological blood pressure lowering reduces dementia incidence.

Based on these findings, we are proposing a follow-up study that will determine how long the "legacy effect" persists for, to better understand the effects of early tight glucose and blood pressure control in patients with newly diagnosed type 2 diabetes on important long-term clinical outcomes.

4. STUDY DESIGN

Extended follow up of a randomised control trial into electronic health records and other routinely collected health data. These record level data will be obtained from NHS Digital (or appropriate equivalent, in the case of the devolved administrations) after all necessary approvals have been granted. The data requested will include, but will not be limited to, Hospital Episode Statistics (HES), mental health data and mortality data from the Office of National Statistics (ONS).

5. STUDY OBJECTIVES

1. To determine whether participants randomly allocated to tight, rather than less tight, blood pressure control have a lower risk of dementia.
2. To determine whether participants randomly allocated to intensive, rather than conventional, glucose control have a lower risk of dementia.
3. To determine whether tight blood pressure control or intensive glucose control reduces the long-term risk of major vascular diseases in diabetes
4. To determine whether tight blood pressure control or intensive glucose control reduces long-term health resource use and total burden of disease in diabetes
5. To investigate use of health care resources in secondary care by patients with diabetes

6. HYPOTHESES

Higher blood glucose measures and other measures of poor diabetes control are associated with a higher risk of dementia, and fatal and non-fatal vascular events

- That this is observed when comparing participants with a higher blood glucose and other measures of diabetes control measured at baseline, and in follow up, to patients with lower blood glucose at those time periods.
- That this is observed in participants randomly allocated to tight blood glucose control compared with patients allocated to less tight blood glucose control, and this effect is proportional to the degree of diabetes control.

Higher mean blood pressure is associated with a higher risk of dementia and fatal and non-fatal vascular events

- That this is observed when comparing participants with a higher mean systolic blood pressure at baseline, and in follow up, to patients with lower mean blood pressure

- That this is observed in participants allocated to a tight blood pressure control compared to patients allocated to an less tight blood pressure control, and the degree of risk increase is proportional to the difference in mean systolic blood pressure
- That this is attenuated after adjusting for non-fatal stroke or TIA

Greater blood pressure variability is associated with a higher risk of dementia and fatal and non-fatal vascular events

- That this is observed when comparing participants with a greater standard deviation of systolic and diastolic blood pressure measurements at baseline, and in follow up, to patients with lower standard deviation of mean blood pressure measurement.
- If a difference is observed between randomly allocated groups, that this is observed in participants allocated to a tight blood pressure control compared to patients allocated to a less tight blood pressure control.
- That this is attenuated after adjusting for non-fatal stroke or TIA

APOE4 risk alleles modify the associations between measures of diabetes control, mean blood pressure and blood pressure variability with and fatal and non-fatal vascular events

- That patients with the risk alleles ε4/ ε4 have a greater risk of dementia than patients with risk alleles ε4/ ε3 and risk alleles ε3/ ε3
- That there is an interaction between the association of mean blood pressure, and blood pressure variability with APOE4 risk alleles, in the direction of a greater relative risk of dementia with greater mean blood pressure/ blood pressure variability in participants with ε4/ ε4.

7. STUDY POPULATION

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

8. INTERVENTION

No further interventions are planned as part of this study.

9. OUTCOME ASCERTAINMENT

We will measure five outcomes in linked electronic health data: dementia, stroke, all major cardiovascular disorders, other diabetes related complications and death. We will link UK participants 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 held by the NHS Digital
2. Scottish Morbidity Record (SMR) and death statistics in Scotland held by Information and Services Division, of NHS Scotland
3. Hospital activity statistics in Northern Ireland, Honest Broker Service, Northern Ireland Statistics and Research Agency (www.hscbusiness.hscni.net).
4. We will using existing data within UKPDS systems and paper records, including previous psychological measures for each participant.

We will define stroke, and dementia as follows:

Stroke

Stroke is 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 only.

Data sources

EHR/death records

We will use the ICD codes set out in appendix B to define stroke of different types. Date of diagnosis will be recorded. Note: no laterality is likely to be available in these records.

Review of records

Two clinicians will adjudicate independently and check for concordance aiming for 100%. A third adjudicator will be involved if there is a disagreement. The clinicians will in their judgement attempt to define the stroke by subtype (if available). Date of diagnosis will be recorded.

Stroke recorded, with subtype, in existing UKPDS analysis dataset.

Definition of stroke

We will define the following cerebrovascular outcomes:

1. First ischaemic stroke post randomisation: the first record and date of an ischaemic stroke in EHR, death record, review of records or UKPDS dataset.

2. First intracerebral haemorrhage post-randomisation the first record and date of an intracerebral haemorrhage in EHR, death record, review of records or UKPDS dataset.

3. First ischaemic or unspecified stroke post-randomisation: the first record and date of an ischaemic stroke or stroke of uncertain cause in EHR, death record, review of records or UKPDS year dataset.

4. First disabling or fatal ischaemic or unspecified stroke post-randomisation: the first record and date of an ischaemic stroke or stroke of uncertain cause in EHR, death record, review of records or UKPDS dataset where death occurred within 30 days of stroke, or modified Rankin recorded as >2.

5. First cerebral ischaemia post randomisation: the first record and date of an ischaemic stroke or TIA or retinal artery occlusion or stroke of uncertain cause in EHR, death record, review of records or UKPDS.

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, we will primarily use all cause dementia. In secondary analysis, should there be sufficient data, we will look at vascular dementia, Alzheimer's dementia and other dementias.

Data sources:

EHR/death records.

Mental health records

Review of UKPDS records – Two clinicians will adjudicate independently and check for concordance aiming for 100%. A third adjudicator will be involved if there is a disagreement. The clinicians will in their judgement attempt to define the dementia by subtype (if available). Date of diagnosis will be recorded. (See appendix B)

Psychological measures: 1276 patients (of 2300 approached) had cognitive testing at the end of the study, and a further cohort of (N) patients had cognition evaluated 3 years later. Information was collected on the Geriatric Depression Scale (GDA), the Symbol Digits Modalities Test, a modified telephone interview for cognitive status and a category fluency test (naming animal in one minute). There is no generally agreed threshold for the diagnosis of dementia on the symbol digits modalities test, though it is the most complete of the psychological tests in UKPDS (97% complete).

Definition of dementia

We will define the date of onset of the primary outcome of dementia as the first record of **any dementia** or cognitive impairment in any one of the five datasets. For the primary outcome, we will use dementia of any type, i.e. Alzheimer's disease, vascular dementia, or other dementia (see appendix)

For secondary analysis we will define the subtype of the first mention of dementia as:

Alzheimer's disease when there is a record of Alzheimer's disease, but no other record at any time of another subtype of dementia (i.e. vascular dementia or rare dementia). Alzheimer's disease will be recorded when in any HES or death records there is a ICD10 code of F00.x or G30.x or ICD9 code 331.0; or where the free text of the death record contains the string "*Alzheimer**"; or where the patient is prescribed a drug associated with dementia (see appendix 3) and this is recorded in the Scottish datasets; or where the review of the UKPDS records indicates Alzheimer's disease is the primary diagnosis.

Vascular dementia as a record of vascular dementia, but no other record at any time of another subtype of dementia (i.e. Alzheimer's disease or rare dementia). Vascular dementia will be recorded where there is a record in any HES or death records there is an ICD10 code of F01x or I67.3, or ICD9 code of 290.4; or where there is a free text string in the death record of "*vascular dementia*" or "*multi-infarct dementia*" or where UKPDS records indicate vascular dementia is the primary diagnosis.

Other dementias as no record of a dementia subtype (i.e. Alzheimer's disease, vascular dementia or rare dementias), or with more than one record of different dementia subtypes, i.e. any of the other codes listed in appendix 1 and 2.

Dementia or EHR signs of cognitive impairment: where in HES records there is a record of admission from or to a **nursing home**, or where the patient has been under the care of **geriatric psychiatry** or any other dementia diagnosis.

Myocardial infarction:

Admissions or deaths: ICD-10 codes: I21-23, I46 (cardiac arrest)

In addition, we will examine for other codes indicating major vascular disease, including (although 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

10. DISSENT

We will exclude participants who have already opted out from having their data stored by NHS Digital. In addition, participants who have read our privacy notice and have decided that they do not wish their data to be used in this study will be able to opt out.

11. STATISTICAL ANALYSES

Analyses 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 outcome of interest (e.g. stroke, myocardial infarction, dementia, mortality) rates between both treatment groups.

11.1. Health Economic Analyses

The economic analyses will be primarily concerned with estimation rather than hypothesis testing. Hospital resource use data will be used to estimate hospital costs per patient/year. Cost data will then be combined with data on occurrence of complications and other patient characteristics to estimate, using appropriate econometric methods (e.g. generalised linear models), the short- and long-term cost consequences of complications, and the overall burden of disease adjusted for the national population with type 2 diabetes. This will be done using hospital contact data (inpatient care, outpatient care, emergency attendance and critical care) which will be grouped into Health Resource Groups (HRGs) according to the diagnosis and procedures recorded for each contact. A National Casemix Office Reference cost Grouper will be used to produce a HRG per contact. The derived HRGs will then be matched with NHS Reference costs to estimate the cost of hospital resource use utilisation and inform the health economic analyses. Reference costs reflect the direct, indirect and overhead costs associated with providing one unit of patient care in a given financial year and are collected from all NHS organisations.

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. All persons handling ONS mortality data will hold valid ONS Researcher Accreditation Status.

Direct access will be granted to authorised representatives from the Sponsor for monitoring and/or audit of the study to ensure compliance with regulations.

12.2. Data Recording and Record Keeping

We will transfer participant identifiers with linked trial id numbers to NHS Digital/ISD through a secure route approved by the receiving bodies. We will receive data back to Oxford in an encrypted format via the Oxford secure data transfer system (https://oxfile.ox.ac.uk). Each participant will be identified by trial identifier only at this stage, not with name, date of birth etc. We will construct a dataset from the original UKPDS trial dataset with covariates for this analysis, where each participant is identified only by the anonymised trial identifier. We will link this dataset with the information received from NHS Digital/ISD with anonymised trial identifiers in the University of Oxford Health Economic Research Unit (HERC), Nuffield Department of Population Health (NDPH).

The data will be stored at the Health Economic Research Unit (HERC), Nuffield Department of Population Health (NDPH) Richard Doll Building, University of Oxford. NDPH has successfully acquired analysed and appropriately stored data from HES for previous large long-term studies such as HPS2-THRIVE and HPS3-REVEAL. NDPH researchers are experienced in handling confidential and participant sensitive data and have appropriate training in information governance.

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 a need to access the required data. Only personnel involved in the long-term follow-up study for UKPDS (processing and analysing data) will have 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. HERC investigators are within NDPH and are fully aligned with all data management and security policies.

Identifiers will need to be retained whilst linkages are made between UKPDS datasets (we anticipate this will take up to a year) before all data are identified primarily with the study ID, in order to pseudo anonymise the long term follow-up dataset. An anonymised dataset will be kept for analysis indefinitely.

13. ETHICAL AND REGULATORY CONSIDERATIONS

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

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

We will not approach participants for further consent, but will seek permission of the Confidentiality Advisory Group of the Health Research Authority of NHS England (CAG 251) and the equivalent bodies in NHS Scotland and Northern Ireland.

We believe this is justified for the following reasons:

1. Approaching participants for consent would be impracticable. Follow-up of health outcomes by mailing annual questionnaires to large numbers of patients and their doctors is costly and cumbersome, as well as resulting in incomplete data. It is for this reason that we seek to obtain access to HES data.

2. Obtaining data from participants directly would lead to unreliable conclusions. Many participants had died by last follow-up (2007). Approaching living participants for consent would lead to such a bias in ascertainment that any conclusions from the linkage study would be unreliable (previous studies have demonstrated that non-responders are more likely to have dementia which would further bias this study).

3. The topic is an important one: the prevention of dementia is a current public health priority, as is the prevention of the major complications associated with type 2 diabetes.

Any study that seeks to answer this question would need to be a sufficiently large trial and would be extremely expensive as well as not making the best use of existing information.

4. We have consulted Patient and Public Involvement (PPI) panels.

The overwhelming majority of participants agreed that this use of data is justified and none expressed strong opposition to this research proposal providing that appropriate measures were in place to protect confidentiality (see appendix C).

14. FUNDING

Diabetes Trials Unit, University of Oxford & Chief Scientist's Office, Scotland

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: DEMENTIA OUTCOME: FILE INVESTIGATION METHODOLOGY

UKPDS Long-term Follow-up: File Investigation Methodology SOP

Databases where data investigated from UKPDS files are stored by Study Coordinator:

Data fields:

- UKPDS study ID
- UK participants breakdown into England & Wales/ N. Ireland/Scotland
- Access database form number
- Any stroke (yes/no) and date
- DOB
- DOD
- Location at death
- Dementia evidence (yes/no)
- Date of Dementia diagnosis
- Review date, reviewer & review outcome
- Type of dementia (if known) Unspecified code only; (Alzheimer's disease (AD) code +/- unspecified; Vascular Dementia (VaD) code +/- unspecified; other codes; mixed codes (AD+VaD)

Methodology of Data Collection:
Each case file (and Major Event file if applicable) is reviewed by the Study Coordinator blinded to the UKPDS randomised treatment allocation.

Any direct evidence of *dementia* or *cognitive impairment* or any reference to *memory problems/forgetfulness/falls/frailty/admission to residential care* is added to the database.

- The source of dementia diagnosis is recorded (*WhereDementiaMentioned*) and date of dementia diagnosis (*DateDementiaMentioned*). If there is no specified date the mid-year first recorded/mentioned e.g. the annual assessment year or outpatient letter should be used.
- For diagnosis of dementia shown on the ONS notification as cause of death the date of death should be recorded.

These cases will then be flagged for clinician review to confirm evidence of dementia or cognitive impairment or to refute the evidence provided.

Cases for Clinician Review: Each participant file is prepared for review. The Clinician Reviewer is blinded to treatment allocation and to the Study Coordinator's review. See the 'Review Form Template.

A) Definition/data required for **dementia diagnosis:**
Should include evidence of dementia on one or more of the following:
1) Listed on death certificate (ONS notification)

2) Documented in the UKPDS case file or Major Event file as 'dementia' from a confirmed source e.g. annual follow-up, clinic appointment, information from relative, post mortem
3) Review of all available UKPDS information

Dementia is then recorded on the review form.

B) If no definite dementia diagnosis but there is evidence of:
1) Mild cognitive impairment (MCI)
2) Cognitive impairment/ poor short-term memory/cognitive decline/other term indicating cognitive problems
3) Delirium

Cognitive impairment is then recorded on the review form.

The Study Coordinator will also pick at random a percentage of cases for clinician review, where A and B do not appear to apply, to determine inter-rater agreement (kappa) for qualitative review and outcome between the Study Coordinator and the Clinician Reviewer.

Once completed with the outcome decision the review form is signed and dated by the reviewer (hard copy) and stored in the Dementia Review Folder.

The outcome decision is added to the Excel and Access database by the Study Coordinator.

UKPDS Dementia Project: Access database FIELD CODES		
	Drop down Menu	**Data Format**
Patients_Randomisation data		
PatientNumber		Free text
Death		
Death:	<Yes	
	<No	
DeathDate:		dd/mm/yyyy
Autopsy:	<Yes	
	<No	
	<unknown	
DeathCause:		Free text
PlaceOfdeath:	<Home	
	<Nursing Home	
	<Hospice	
	<Hospital	
	<Unknown	
Reported:	<Clinician	

	<Relative/friend	Multiple options can be selected
	<Major Event Classification	
	<ONS notification	
	<ASCT-1 File	
	<Not recorded	
DeathAddInfo:		Free text
Dementia		
Dementia:	<Yes	
	<No	
DateDementiaMentioned:		dd/mm/yyyy
WhereDementiaMentioned:	<Patient/relative	Multiple options can be selected
	<ASCT-1 file	
	<Major Events docs	
	<ONS notification	
	<Annual follow-up	
	<Other	
UKPDS Dementia Project: Access database FIELD CODES		
ProofDementiaConfirmed:	<Clinical Notes	Multiple options can be selected
	<CT/MR imaging	
	<Autopsy	
	<GP	
	<Cognitive assessment	
	<Other	
	<Blinded Physician Review	
DiagnosisDementiaDate:		dd/mm/yyyy
TypeOfDementia:	<Vascular	
	<Alzheimer's	
	<Assoc w.neuro-diagnosis (e.g. Parkinson's)	
	<Dementia + delirium	
	<Unspecified/other	
DementiaAddInfo:		Free text
Stroke		
Stroke:	<Yes	
	<No	
NumberOfStrokes:		Free text
DateOfFirstStroke:		dd/mm/yyyy
FirstStrokeSide:	<Left	
	<Right	
	<Midline	

	<Cortical lesion	
	<Unknown	
FirstStrokeRankinScore:	<Disabling	
	<Good outcome	
	<0	
	<1	
	<2	
	<3	
	<4	
	<5	
	<Fatal stroke	
	<Unknown	
DateOfWorstStroke:		dd/mm/yyyy
WorstStrokeSide:	<Left	
	<Right	
	<Midline	
	<Cortical lesion	
	<Unknown	
WorstStrokeRankinScore:	<Disabling	
	<Good outcome	
	<0	
UKPDS Dementia Project: Access database FIELD CODES		
WorstStrokeRankinScore:	<1	
	<2	
	<3	
	<4	
	<5	
	<Fatal stroke	
	<Unknown	
StrokeAddInfo:		Free text
More Info		
Medication:	<Antiplatelet	Multiple options can be selected
	<Stain/Lipid lowering	
	<Antihypertensive	
	<Anticoagulant	
	<None	
	<Unknown	
EvidenceOfAF:	<Yes	
	<No	
AF-YearFirstRecorded:		Free text
Diabetes:	<Yes	
	<No	
Diabetes-YearFirstRecorded:		Free text

BP- ever 160/90:	<Yes	
	<No	
MI:	<Yes	
	<No	
DateOfMI:		dd/mm/yyyy
HeartFailure:	<Yes	
	<No	
HeartFailure-YearFirstRec:		Free text
Anxiety:	<Yes	
	<No	
Education Level:	<Lower secondary	
	<Upper secondary	
	<First Degree	
	<Master or eq.	
	<Doctoral or eq.	
	<Unknown	

Long-term follow-up: Dementia project

Participant file review

UKPDS Participant study ID:

Date of Review:

Comments:

Outcome decision:

Dementia: ☐ yes ☐ no Cognitive impairment: ☐ yes ☐ no

Other:_____

Type of Dementia if known: Date of dementia diagnosis:

Source of dementia/cognitive information:

ICD code:

Reviewer name :_____

Signature:_____

18. APPENDIX B ICD codes for outcomes of interest

ICD-9 and ICD10 codes for dementia

ICD-10

	Alzheimer's disease
F00	Dementia in Alzheimer's disease
F000A	Dementia in Alzheimer's disease with early onset
F001A	Dementia in Alzheimer's disease with late onset
F002A	Dementia in Alzheimer's disease, atypical or mixed type
F009A	Dementia in Alzheimer's disease, unspecified
G30	Alzheimer's disease
G30.0	Alzheimer's disease with early onset
G30.1	Alzheimer's disease with late onset
G30.8	Other Alzheimer disease, unspecified
G30.9	Alzheimer's disease unspecified
	Vascular dementia
F01	Vascular dementia
F010	Vascular dementia of acute onset
F011	Multi-infarct dementia
F012	Subcortical vascular dementia
F013	Mixed cortical and subcortical vascular dementia
F018	Other vascular dementia
F019	Vascular dementia, unspecified
I67.3	Binswanger's disease
	Rare dementia
F020A	Dementia in Pick's disease
F021A	Dementia in Creutzfeldt-Jakob disease
F022A	Dementia in Huntington's disease
F023A	Dementia in Parkinson's disease
F024A	Dementia in human immunodef virus [HIV] disease
F028A	Dementia in other specified diseases classified elsewhere
	Unspecified dementia type
F02	Dementia in other diseases classified elsewhere
F03X	Unspecified dementia
F051	Delirium superimposed on dementia
	Possible dementia
F050	Delirium not superimposed on dementia, so described
F058	Other delirium
F059	Delirium unspecified
G31.0	Circumscribed brain atrophy
G31.1	Senile degeneration of brain, not otherwise classified
G31.2	Degeneration of nervous system due to alcohol
G31.8	Other specified degenerative diseases of nervous system
G31.9	Degenerative disease of nervous system, unspecified

ICD-9

	Alzheimer's disease
331.0	Alzheimer's disease
	Vascular dementia
290.4	Vascular dementia
	Rare dementia
046.19	Creutzfeld Jacob
333.4	Huntingdon's
331.1	Frontotemporal dementia
	Unspecified dementia type
290.0	Senile dementia, uncomplicated
290.1x	Presenile dementia
290.2	Senile dementia with delusional features
290.3	Senile dementia with delirium
	Possible dementia
294.9	unspecified persistent mental disorders
331.2	Senile degeneration
331.9	Cerebral degeneration unspecified

ICD-10 and ICD9 codes for stroke and TIA

ICD9	**ICD-10**	
362.3	H34.1	Central retina artery occlusion
433.x1, 434.x1	163.x	Cerebral infarction
436	I64.x	Stroke, no specified
431.x	I61.x	Intracerebral haemorrhage
430.x	I60.x	Subarachnoid haemorrhage
435.x	G45.x	Transient ischaemic attack and related syndromes

Dementia drug codes

Acumor XL 16mg m/r capsules
Acumor XL 24mg m/r capsules
Acumor XL 8mg m/r capsules
Aricept 10mg tablets
Aricept 5mg tablets
Aricept Evess 10mg oro-dispersible tablets
Aricept Evess 5mg oro-dispersible tablets
Donepezil hydrochloride 10mg oro-dispersible tablets
Donepezil hydrochloride 10mg tablets
Donepezil hydrochloride 5mg oro-dispersible tablets

Donepezil hydrochloride 5mg tablets
Ebixa 10mg/g oral drops
Ebixa 20mg tablets
Elmino XL 16mg m/r capsules
Elmino XL 24mg m/r capsules
Elmino XL 6mg m/r capsules
Exelon 9.5mg/24hrs patches
Galantamine 12mg tablets
Galantamine 16mg m/r capsules
Galantamine 24mg m/r capsules
Galantamine 4mg tablets
Galantamine 4mg/ml s/f oral solution
Galantamine 8mg m/r capsules
Galantamine 8mg tablets
Galsya XL 16mg m/r capsules
Galsya XL 24mg m/r capsules
Galsya XL 8mg m/r capsules
Lotprosin XL 16mg m/r capsules
Lotprosin XL 24mg m/r capsules
Lotprosin XL 8mg m/r capsules
Memantine hydrochloride 10mg tablets
Memantine hydrochloride 20mg
Reminyl 12mg tablets
Reminyl 4mg tablets
Reminyl 4mg/ml s/f oral solution
Reminyl 8mg tablets
Reminyl XL 16mg m/r capsules
Reminyl XL 24mg m/r capsules
Reminyl XL 8mg m/r capsules
Rivastigmine 1.5mg capsules
Rivastigmine 2mg/ml oral solution
Rivastigmine 3mg capsules
Rivastigmine 4.5mg capsules
Rivastigmine 4.6mg/24hrs patches
Rivastigmine 6mg capsules
Rivastigmine 9.5mg/24hrs patches
Ebixa 10mg tablet
Memantine hydrochloride 10mg/g oral drops
Ebixa treatment initiation pack tablets
Nemdatine 10mg tablets
Nemdatine 20mg tablets
Exelon 1.5mg capsules
Exelon 3mg capsules
Exelon 4.5mg capsules
Exelon 6mg capsules
Exelon 2mg/ml oral solution
Exelon 4.6mg/24hrs patches
Exelon 9.5mg/24hrs patches
Rivastigmine 13.3mg/24hrs transdermal patches
Nimvastid 1.5mg capsules

Nimvastid 3mg capsules
Nimvastid 4.5mg capsules
Nimvastid 6mg capsules
Exelon 13.3mg/24hrs transdermal patches
Alzest 4.6mg/24hrs transdermal patches
Alzest 9.5mg/24hrs transdermal patches
Prometax 4.6mg/24hrs transdermal patches
Prometax 9.5mg/24hrs transdermal patches
Somniton 4.6mg/24hrs transdermal patches
Somniton 9.5mg/24hrs transdermal patches

19. Appendix C: Comments from Oxford Centre for Diabetes, Endocrinology and Metabolism PPi panel

	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 should be supported. Any reduction that can be made in the number of diabetic amputations should be actively promoted	It seems sensible to me to that we study if the risk of complications (for T2D) can be reduced by the use if certain medications and what the benefits might also be.	It is well known that poorly controlled diabetes increases 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	If a correlation between long term blood glucose 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 furthe 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	

Responses from prevous PPi panels for previous long term follow studies

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 for UKPDS long-term follow-up is similar to those required for the HPS2-THRIVE study, 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. We also surveyed five patient and public panels to test the acceptability of follow up into electronic health records of participants from old randomised controlled trials that were designed before long-term follow up into electronic health records was thought to be routinely feasible. We consulted the following panels:

1. NIHR Stroke Research Network Panel

2. Clinical trials support unit, University of Oxford

3. University College London PPi group

4. ASCOT participants PPi group]

5. OCDEM PPi Group

We asked participants:

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 2/34 (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: 27/34 (75%)

No: 3/34 (6%)

Unsure 6/34 (17%)

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

Yes: 24/35 (69%)

No: 4/34 (14%)

Unsure 6/34 (18%)

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

Yes: 6/35 (17%)

No: 26/35 (72%)

Unsure 4/35 (11%)

We have in addition consulted with participants from the ASCOT trial about a similar project

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 through the project was a good idea. Some representative comments:

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

"It make 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 results 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 reseach 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.