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ADDITION:
5-yr follow-up study

MRC | Epidemiology Unit

1. Study title

Anglo-Danish-Dutch study of Intensive Treatment of people with Newly diagnosed diabetes in primary care (ADDITION)–five year follow-up

2. Investigators

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3. Background to the study

People with type 2 diabetes mellitus are at increased risk of developing micro- and macrovascular complications [1, 2] and of substantial reduction in life expectancy [3]. The onset of this increased risk predates the point of clinical recognition by several years [4] such that at diagnosis approximately 50% of people have evidence of diabetes related complications [5, 6]. Given the high prevalence of undiagnosed diabetes [7] and the evidence of effectiveness of intensive treatment in reducing risk of complications among people with clinically diagnosed diabetes [8-15], screening and earlier initiation of such treatment has been the subject of considerable debate [16-21].

Our review of the evidence for screening for the UK National Screening Committee (NSC), highlighted important uncertainties about cost-effectiveness and potential adverse consequences [22]. As a result of this work we were funded by the NSC to build a public health model in collaboration with the MRC Biostatistics Unit. This study suggested that a critical but unknown parameter in assessing the balance between the costs and benefits of diabetes screening was the magnitude of cardiovascular risk reduction following early detection and intensive therapy. Anticipating this result, we had previously established in the UK, Denmark and Netherlands, a large randomised controlled trial of intensive multi-factorial therapy in people with screen-

detected diabetes in general practice. The UK arm of the trial was funded by the Wellcome Trust, the MRC and NHS Research and Development support and allowed the establishment of the study and re-measurement of 85% of screen-detected patients at one year. Maintenance of the intervention is continuing but we now need to seek funding for follow-up to 5 years (i.e. 2009) and the central co-ordination and analysis of the trial outcome data. This proposal briefly outlines results which have already been generated by the *ADDITION* study and sets out the aims and coordination of a five-year follow-up of *ADDITION* trial participants.

Findings of the ADDITION trial

The Anglo-Danish-Dutch Study of Intensive Treatment of people with newly diagnosed diabetes in primary care (*ADDITION)* study was set-up in 2001. It is a primary care-based study consisting of a screening phase followed by a pragmatic open-label cluster randomised controlled trial comparing the effect on cardiovascular risk of intensive multi-factorial therapy with standard care in patients with screen-detected diabetes.

Following a step-wise screening programme, participants identified with type 2 diabetes were cluster-randomised by practice to intensive multi-factorial therapy with standard care (IT) or routine care (RC) according to current national guidelines, and were followed for one year. The principal outcome was modelled cardiovascular risk. The ADDITION study has so far led to the publication of 19 papers, with a further 12 under review or in press. Data from ADDITION has contributed to 7 PhD theses, and 48 oral presentations or posters at international conferences.

Preliminary results from the ADDITION trial are summarised below:

- Baseline data from both the Cambridge and Danish-ADDITION studies showed that screen-detected diabetes patients exhibit an adverse cardiovascular risk profile [23, 24]. In the Cambridge-ADDITION trial, 35% of participants with hypertension were not prescribed drugs and 42% were sub-optimally treated. Similarly, in participants with dyslipidemia, 69% were not prescribed a therapy and 18% were poorly controlled. Modelling work showed that absolute CVD risk reduction (6.6%) was possible through early intensive pharmacological intervention using relative risk reductions for individual therapies from published trials [23].
- A controlled trial of the psychological impact of stepwise screening for diabetes was embedded in the ADDITION-Cambridge trial [25, 26]. State anxiety, depression, worry about diabetes and self-rated health were compared in those participants invited to screening and those not invited (controls). No significant differences were found between the screening and control participants at any time in the stepwise programme, suggesting that screening for type 2 diabetes has limited psychological impact on patients.
- CVD risk factors in both the Cambridge and Dutch-ADDITION studies showed an improvement between the IT and RC arms. In the Dutch-ADDITION trial, participants in the IT arm had significantly lower levels of BMI, systolic and diastolic blood pressure, HbA_{1c}, total cholesterol and LDL-cholesterol after one year [27]. SF-36 and health-related quality of life scores between the treatment groups were not significantly different. In the Cambridge-ADDITION trial, there were significant improvements in HbA_{1c}, systolic and diastolic blood pressure, total cholesterol and LDL cholesterol in the IT arm after one year [28].

Overall, these results suggest that the cardiovascular profile of people with screen-detected diabetes is improved by early intensive risk factor management. Cardiovascular risk factors improved between diagnosis and follow-up and were significantly lower among intensively treated patients [28]. Furthermore, there appear to be limited psychological harms associated with screening. While these results suggest that screening for diabetes might be worthwhile, the magnitude of cardiovascular risk reduction following early detection and intensive therapy in the

long-term remains unclear. The potential reduction in hard clinical endpoints, such as cardiovascular mortality, heart attack, stroke, amputation and revascularisation, is important to quantify. As such, we plan to follow-up all ADDITION-participants at five years to establish the effectiveness and cost-effectiveness of the intervention. We believe that this trial is critical to future policy-making. Indeed at a recent ADA/EASD international consensus workshop on screening, it was noted to be a critical study globally.

Summary of proposal

We plan to contact all *ADDITION* participants who were diagnosed with type 2 diabetes as a result of the original screening study for a health assessment five years post-randomisation (n=867). Original recruitment and retention of trial volunteers was very high, with 74% of those invited to screening attending an initial appointment, and 85% of those agreeing to take part in the trial of intensive versus routine care attending for their one-year assessment, so we hope to achieve a good response rate. The follow-up study will allow a trial analysis of long term effects of the intervention on cardiovascular morbidity and mortality, as well as revascularisation and amputation rates between the two groups. It will also afford the ability to examine which process measures are associated with reduced cardiovascular risk. The five-year follow-up study will be run concurrently across all three countries and study centres participating in the ADDITION trial (Cambridge and Leicester, Denmark, and the Netherlands).

4. Aims of the study

We aim to follow-up *ADDITION* trial participants to quantify the effectiveness and cost-effectiveness of intensive treatment of screen-detected type 2 diabetes patients. The *ADDITION* trial international steering committee has agreed that the MRC Epidemiology Unit should lead the 5-year follow-up, the assessment of cost-effectiveness and the public health modelling of the implications for policy-making. Agreed endpoints are summarised below. Outcome ascertainment methods are outlined in Appendix 2.

Primary endpoints

1.0 Cardiovascular mortality
2.0 Cardiovascular morbidity
- 2.1 Myocardial infarction (non fatal)
- 2.2 Stroke (non fatal)

3.0 All revascularisations (except for traumatic)
4.0 Amputations

Secondary endpoints

1.0 All cause mortality
2.0 Development of renal impairment
3.0 Development of eye complications
- 3.1 Progression of retinopathy
- 3.2 Macular oedema
- 3.3 Reduced visual acuity
- 3.4 Blindness

4.0 Diabetic ulcer
5.0 Health economy
- 5.1 Patient costs
- 5.2 Health service costs

6.0 Perceived health
- 6.1 Health status
- 6.2 Quality of life
- 6.3 Patient satisfaction
- 6.4 Health utility

Intermediate endpoints

Changes in:

1.0 Self-reported smoking status
2.0 Self-reported dietary behaviour
3.0 Self-reported physical activity
4.0 Self-reported medication adherence
5.0 Haemoglobin A_{1c}
6.0 Total cholesterol
7.0 LDL-cholesterol
8.0 HDL-cholesterol
9.0 Triglycerides
10.0 Blood pressure
11.0 Modelled cardiovascular risk (UKPDS v3)

5. Methods

5.1 ADDITION

Full details of the original study design can be found elsewhere [29]. Ethical approval was obtained from the Eastern Regional Ethics Committee (reference number: 02/5/54). Participants gave written informed consent to take part in the study.

Participants

Eligibility criteria included: age (40-69yrs) with a diabetes risk score above the pre-determined cut-off (>0.17, the top 25% of the risk distribution) and subsequent diagnosis of type 2 diabetes following screening in the *ADDITION* programme. Exclusion criteria include women who are pregnant or lactating or anybody who has a psychotic illness or an illness with a likely prognosis of less than one year.

Intervention

Patients with screen-detected diabetes were cluster-randomised to one of two interventions: routine care according to current national guidelines or intensive treatment. The following features were added to existing diabetes care to achieve intensive treatment:

- Additional NHS R&D Support for Science funding to facilitate more frequent contact between patients and practitioners and to facilitate dietician referrals for all newly diagnosed patients
- Three practice-based education sessions with the local diabetologist
- Patient education materials providing a shared framework on the causes, consequences and treatment of diabetes
- Management algorithms specifying prescription of an angiontensin converting enzyme inhibitor (ACE) and aspirin, followed by stepwise target-led treatment to reduce hyperglycaemia, blood pressure, hyperlipidaemia and microalbuminuria
- Provision of glucometers for patients and any necessary training in their use for practitioners

The funding for practices aimed to facilitate one annual review, five additional consultations with a GP and seven with a nurse, per year for the first three years after diagnosis, over and above the usual consultation frequency for a patient with diabetes aged 40 to 69 years. In the initial educational session for practitioners the justification for intensive treatment was described and the treatment targets and algorithms and patients materials discussed with support from the local specialist. There were two further sessions, six and twelve months later, and these were more interactive and involved discussion about optimising the management of individual study participants. Each intensive treatment practice has subsequently been visited four times over the previous five years to discuss individual participants and keep GPs and practice nurses engaged with the intervention. The patient education materials (Getting Started with Diabetes) were developed by a multidisciplinary team and draw on Leventhal's self regulation model, a social cognition model from psychology [30]. The materials cross-refer to 'Diabetes for Beginners Type

2' a Diabetes UK publication (www.diabetes.org.uk), which was also be included in the information pack for all new patients. The treatment targets and management algorithms are based on recent trial data demonstrating the benefits of intensive treatment of several cardiovascular risk factors in people with diabetes [13, 31]. All patients without specific contraindications were advised to take 75 mg aspirin. Those with a previous cardiovascular event or at least one other cardiovascular risk factor were prescribed an angiotensin converting enzyme (ACE) inhibitor [13]. The rest of the intervention was based on the stepwise regime from the Steno study [14] aimed at optimising hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria. Although targets for treatment were specified and classes of drugs recommended, where there was a choice of individual agents the decision was made by the GPs and patients.

5.2 Follow-up health assessment

We propose a similar design to the original one-year follow-up assessment. All participants (n=867) will initially be contacted with a newsletter outlining the main study results and our plans to invite them back for a five-year follow-up appointment. The newsletter will include details about the comprehensive health check and summary report participants will receive if they take part in the research. In a second letter participants will then be invited for a follow-up health check, the details of which are outlined below. All travel and parking expenses will be reimbursed.

5.3 Logistics

Location: Ely, Cambridge and Wisbech MRC Epidemiology research facilities. If a participant is unable to travel to one of the research facilities, we will try to visit their home or GP to collect follow-up measurements if the participant agrees.

Study coordination: JM and trial coordination team (KW, JG, FW) to meet every two weeks. Study progress meetings will take place monthly (JM, KW, SJG and RKS). Small monthly meetings in the field epidemiology team. Larger PI meetings, including SJG, RKS and field epidemiology teams to meet quarterly.

Measurements (see Appendix 1 for full table of proposed measures):

- Questionnaires: IPAQ, EPQA2, a general health questionnaire including questions on medication, CVD morbidity, smoking and alcohol consumption, SF36 (quality of life / health status), FFQ (food frequency questionnaire), MARS (medication adherence), EuroQol EQ-5D (health utility), ADDQol (diabetes dependent quality of life), diabetes treatment satisfaction, W-B Q28 (diabetes well-being), health service costs, Michigan neuropathy
- Anthropometry: height, weight, waist, fat percentage
- Non-fasting blood: glucose, insulin, HbA_{1c}, TC, LDL, HDL, TG, U+Es, Na, K, Urea, Creatinine
- Urine
- Blood pressure, pulse, ECG

We plan to seek ethical and R&D approval from the Cambridge local ethics boards.

Quality assurance: blood and urine samples will be sent to a single Danish laboratory to assess inter-lab variation between the three participating countries. All staff taking anthropometric and physical activity measures at MRC Epidemiology research facilities are trained and follow standard operating procedures. Double data entry of all anthropometric and questionnaire measures will be undertaken by an experienced, independent agency, blind to study group (Wyman Dillon Research and Data Management, Bristol, UK).

All statistical analyses will be supervised by post-doc statisticians in the MRC Epidemiology Unit. The benefits and costs of intensive treatment will be assessed using an intention to treat analysis. Analysis will allow for clustering of patients by practice. The 5-year risk of primary and secondary outcomes will be computed and compared, along with individual outcomes, between screen-detected patients receiving routine (RC) and intensive care (I), adjusting for differences in baseline variables. Sensitivity analyses, assuming a range of outcomes for non-completers will be informed by baseline data. Will Hollingworth (MRC/NHS Post-doctoral Training Fellow, Departmental health economist) will advise on analysis of the cost, health utility and functional status data. The primary perspective for cost analysis will be the health service, with personal patient cost a secondary perspective. The costs of intensive intervention will be compared with unit change in health utility at five years. In addition, costs at five years and future costs derived from existing data will be compared with modelled risk of death and cardiovascular events, with appropriate sensitivity analysis.

5.4 Outcome ascertainment

For the primary endpoints, a number of strategies will be used including self-report of CVD morbidity at the five-year measurement visit, electronic READ code search of medical records for events and notes extraction on potential cases of events. Case report packs will be prepared for independent review of each potential event. All participants are tagged with the Office of National Statistics for ICD-10 coded mortality (Appendix 2).

6. Power

Following blood testing of 76,308 people from 334 practices in the UK, Denmark and the Netherlands, we have recruited 3,057 patients and are powered to detect a 25% reduction in cardiovascular outcomes, with 95% confidence and 80% power, by the anticipated trial end date of 2009.

7. Dissemination of research results

The results of the *ADDITION* 5-yr follow-up study will be disseminated to the academic community through peer-reviewed publications and by presentation at national and international meetings.

Findings will also be summarised in an appropriate form for the service community with the specific aim of suggesting further, applied research and offering recommendations where possible. We plan to produce a summary of findings and distribute to all *ADDITION* participants in the form of a lively newsletter that will mirror the communication previously used to recruit participants.

10. References

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Appendix 1: Proposed measures for *ADDITION* 5-yr follow-up (Cambridge)

Outcome measure	**Baseline**	**1 yr (RC & I)**	**5 yr f-up**
Modelled CVD risk: UKPDS[32]	✓	✓	✓
Fasting, 30 and 120 min venous whole blood HemoCue glucose	✓		
Fasting, 30 and 120 min plasma glucose	✓		
Fasting, 30 and 120 min insulin	✓		
Fasting, 30 and 120 min NEFA	✓		
Non-fasting blood			✓
EDTA tube for DNA extraction	✓		
U+Es, Na, K, Urea, Creatinine	✓	✓	✓
Albumin, Bilirubin, Alanine transaminase (ALT), Alkaline Phosphatase, Aspartate transaminase (AST), Creatine kinase (CK)	✓	✓	✓
Thyroid-stimulating hormone (TSH)	✓		✓
Glycated haemoglobin: ion-exchange liquid chromatography (Tosoh)	✓	✓	✓
Total, HDL and LDL cholesterol and triglyceride	✓	✓	✓
Urinalysis	✓	✓	✓
Urine albumin/creatinine ratio: spot urine	✓	✓	✓
Overall level/regional distribution of body fat: body fat impedance (TANITA scale)	✓	✓	✓
Waist circumference: cm	✓	✓	✓
Weight: TANITA scales calibrated tri-yearly	✓	✓	✓
Height: rigid stadiometer with Frankfort plane horizontal	✓		✓
Blood pressure: OMRON M4 automatic sphygmomanometer	✓	✓	✓
Electrocardiogram	✓	✓	✓
Stereoscopic fundal photography	✓	✓	✓
Frequency of consultations: notes review and self report		✓	✓
Recorded history of cardiovascular events: notes review/PRIMIS search of EMIS notes/ONS tagging for mortality		✓	✓
Anxiety: Spielberger State-Trait Anxiety Inventory [33]	✓	✓	✓
Health utility: EuroQoL EQ-5D questionnaire [34]	✓	✓	✓
Diabetes dependent Quality of life: ADDQoL [35]		✓	✓
Diabetes treatment satisfaction [35]		✓	✓
Diabetes wellbeing (W-B Q28) [35]		✓	✓
Diabetes knowledge [35]		✓	✓
Functional health status: SF-36 Health Survey [36]		✓	✓
Self-reported smoking and alcohol status: general questionnaire	✓	✓	✓
Demographic characteristics: general questionnaire	✓		✓
Personal patient costs (adapted from HSRU Aberdeen) [37]	✓		✓
Health Service costs (adapted from HSRU Aberdeen) [38]		✓	✓
Self-reported history of angina, heart attack or stroke: general questionnaire	✓	✓	✓
Michigan Neuropathy questionnaire (adapted): general questionnaire	✓	✓	✓
Physical activity questionnaire: IPAQ,[39] EPAQ2	✓	✓	✓
Self-reported current medication: general questionnaire	✓	✓	✓

Appendix 2: Outcome ascertainment methods for ADDITION 5-yr follow-up (Cambridge)

PRIMARY ENDPOINTS	**ASCERTAINMENT METHOD**
1.0 Cardiovascular mortality	1. Self-report at five-year measurement visit 2. Electronic READ code search of medical records for events 3. Note extraction on potential cases of events 4. Preparation of case report packs for independent review of each potential event 5. ONS tagging for ICD-10 coded mortality
2.0 Cardiovascular morbidity	
2.1 Myocardial infarction (non fatal)	
2.2 Stroke (non fatal)	
3.0 All revascularisations (except for traumatic)	
4.0 Amputations	
SECONDARY ENDPOINTS	
1.0 All cause mortality	ONS tagging for ICD-10 coded mortality
2.0 Development of renal impairment	Plasma creatinine and urine alb/creat ratio from five-year measurement visit.
3.0 Development of eye complications	Digital retinal image from routine annual examination for independent review (following READ code search in medical records); visual acuity examination?
3.1 Progression of retinopathy	
3.2 Macular oedema	
3.3 Reduced visual acuity	
3.4 Blindness	
4.0 Diabetic ulcer	Michigan neuropathy questionnaire
5.0 Health economy	Questionnaire on recent use of health services (GP / nurse, hospital appointments and admissions) and prescribed medication in the previous 3 months
5.1 Patient costs	
5.2 Health service costs	
6.0 Perceived health	Single item Likert scale (general health status), SF-36, EuroQol, ADDQoL, DTSQ, WBQ-12
6.1 Health status	
6.2 Quality of life	
6.3 Patient satisfaction	
6.4 Health utility	
INTERMEDIATE ENDPOINTS	
Changes in:	
1.0 Self-reported smoking status	General health questionnaire
2.0 Self-reported dietary behaviour	FFQ
3.0 Self-reported physical activity	EPAQ2, IPAQ. 239 IT participants also have individually calibrated heart rate monitoring
4.0 Self-reported medication adherence	MARS questionnaire. Serum levels assessed at one year in 239 IT participants
5.0 Haemoglobin A_{1c}	Addenbrooke's lab using standard assays
6.0 Total cholesterol	
7.0 LDL-cholesterol	
8.0 HDL-cholesterol	
9.0 Triglycerides	
10.0 Blood pressure	Three measures on electronic sphygmomanometer
11.0 Modelled cardiovascular risk	UKPDSv3