

# FREMANTLE DIABETES STUDY

## PHASE II

### Study protocol

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## **AIMS**

1. To build on the original (Phase I) Fremantle Diabetes Study (FDS) by recruiting all consenting diabetic patients in the same catchment area in order to perform a detailed comparison of prevalence, care, control and complications in 2008-2012 to those in 1993-2001.
2. To provide novel long-term data on survivors with type 1, type 2 or latent autoimmune diabetes of adults (LADA) from Phase I, especially in relation to i) risk factors for, and progression of, micro- and macroangiopathy, ii) important non-standard complications identified through Phase I such as osteoporosis, reduced pulmonary function, cognitive impairment and depression.
3. To extend, in a subset of patients, the range of analyses to novel vascular risk factors not measured in Phase I such as highly-sensitive C-reactive protein (hs-CRP), adiponectin, advanced glycation end-products (AGE), homocysteine, plasminogen activator inhibitor-1 (PAI-1) and N-terminal prohormone brain natriuretic peptide (NT-proBNP).
4. To assess bottom-up, patient-level, diabetes-attributable costs from a societal perspective.

## **HYPOTHESES**

1. From Aim 1, i) the prevalence of diabetes is increasing in urban Australia; ii) glycaemic control is not improving despite the benefits of intensive treatment and a greater range of effective therapies; iii) macrovascular disease rates are declining with greater use of cardiovascular therapies but, because of difficulties attaining good glycaemic control, this is not the case for microangiopathy; v) diabetes costs are increasing disproportionately to the increase in prevalence.
2. From Aim 2, i) intensive vascular risk factor management early in the course of diabetes protects against the development of chronic complications; ii) rates of progression of complications do not decrease with time (i.e. there is no plateau effect).
3. From Aim 3, clinically important associations between novel biochemical risk markers and vascular complications found in published clinic- and intervention trial patient samples are confirmed in a community-based diabetic cohort.
4. From Aim 4, more intensive treatment of newly-diagnosed diabetes increases pharmaceutical costs but lessens longer term-costs for hospitalization and residential aged care.

## **BACKGROUND**

The need for natural history studies of diabetes is clear from their potential to provide important data relating to i) prevalence and incidence of diabetes and its major complications, ii) adequacy of current management (from education to therapy) viewed against therapeutic targets, iii) effects on quality of life (QoL), mood, cognition and activities of daily living (ADL), and iv) direct and indirect diabetes costs, including identification of groups who may be disadvantaged or in need of additional interventions that can improve outcome. Such data should have an essential role in health education, the formulation of diabetes-specific management guidelines and pathways, directing clinical audit, and in informing current and future health care planning for diabetes services.

### **The particular need for the FDS**

When Phase I was conceived in 1991, there were few published diabetes natural history data. Population studies such as Framingham<sup>1</sup> and Busselton<sup>2</sup> contained relatively small sub-groups (<400) from which limited additional diabetes-specific information was collected. The United Kingdom Prospective Diabetes Study (UKPDS) had recruited >5,000 newly-diagnosed type 2 subjects aged 25-65 years but the sample was not community-based and the study was interventional with outcomes presented in 1998<sup>3</sup>. There were also Australia-specific aspects of diabetes that had not been characterised in detail, especially the disproportionately large number of patients from a migrant background<sup>4</sup> and the important question of diabetes in indigenous groups<sup>5</sup>.

### **Phase I implementation**

The aim of Phase I was to identify from all potential sources, and collect detailed prospective data from, known diabetic patients in a stable urban population<sup>6</sup>. Based on seeding funding, and respecting reasonable patient time commitment, it was decided to recruit all consenting patients from the Fremantle Hospital (FH) primary catchment area, a postcode-defined population of ~120,000, to yearly assessments of important aspects of diabetes. Of 2258 subjects identified during registration between 1993 and 1996, 1426 (63%) were recruited. This compares favourably with the Australian Diabetes, Obesity, and Lifestyle (AusDiab) Study which recruited 40.9% of randomly-selected households and obtained biomedical data from 56% of identified individuals within them<sup>7</sup>. Detailed FDS assessments continued until 2001, at which time attrition through death, disability and relocation had become significant. Through the WA Data Linkage System (WADLS)<sup>8</sup>, additional morbidity/mortality data were obtained. A range of baseline and outcome data was also collected from the 832 patients who were identified but not recruited to provide an objective assessment of the representative nature of the sample. The need for Phase I has been justified by 47 papers on a range of diabetes-related topics that have appeared in peer-reviewed journals since 1997, with 4 associated editorials.

### **Phase I major findings**

Phase I major findings cover many areas. The first published analyses found that diabetes protects against abdominal aortic aneurysms (AAA) in older men<sup>9</sup>, an observation confirmed later in larger population-based studies. LADA prevalence in the FDS cohort was less than half that in UKPDS and other Northern European studies<sup>10</sup>, reflecting the younger age of UKPDS patients and the relatively large number of Southern Europeans (SE) in the FDS. The type 2 SE patients had worse glycaemic control than the majority Anglo-Celt (AC) group despite greater insulin use and after adjustment for confounders such as diabetes duration and body mass index (BMI), suggesting ethnicity-related differences in pathophysiology<sup>11</sup>. We found that the lung is damaged by diabetes<sup>12</sup> in direct relation to glycaemic exposure<sup>13</sup>. The presence of carotid bruit, an easily detectable sign, proved to be a strong predictor of stroke amongst type 2 patients<sup>14</sup>, while serum HDL-cholesterol was the strongest modifiable predictor of first stroke in type 1 subjects<sup>15</sup>. Analyses have also confirmed that silent myocardial infarction is common in diabetes but that the prognosis in such patients is better than in those with symptomatic presentations<sup>16</sup>. Other papers have reported data demonstrating that the ankle-brachial index (ABI) cut-point of 0.90 for peripheral vascular disease recommended in the general population is also prognostically appropriate in type 2 diabetes<sup>17</sup>, that asymptomatic bacteruria is a strong risk<sup>18</sup> and that osteoporosis risk is increased in young, type 1 males<sup>19</sup>. The most recent and perhaps most contentious findings relate to self monitoring of blood glucose (SMBG) which was not associated with better glycaemic control<sup>20</sup> and, in contrast to other published data, was not protective against complications<sup>21</sup>.

### **New data from other studies**

During Phase I, the results of a number of studies providing data relating to epidemiology and management were published. Locally, AusDiab highlighted the continued increase in diabetes prevalence identified by active screening of individuals aged  $\geq 25$  years (during the 19 years from the Busselton survey<sup>2</sup> to AusDiab in 2000,<sup>7</sup> the increase was 0.15%/year in males and 0.18%/year in females) and the incidence of type 1 diabetes is similarly increasing<sup>22</sup>. The first intervention study with implications for management of Phase I patients was the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes which confirmed the benefits of tight glycaemic control in the prevention of micro-<sup>23</sup> and, more recently, macrovascular<sup>24</sup> disease. The UKPDS results in type 2 patients, which largely paralleled those of the DCCT but which included a hypertension treatment sub-study, followed<sup>3, 25, 26</sup>. Landmark trials such as the Heart Protection Study (HPS)<sup>27</sup> and the Heart Outcomes Prevention Evaluation (HOPE and MICRO-HOPE)<sup>28</sup> provided further evidence of the benefits of intensive vascular risk factor management in type 2 diabetes. Although, consistent with NHANES data from the US<sup>29</sup>, recent FDS analyses do not show that the findings of the UKPDS are influencing glycaemic management in Australia<sup>30</sup>, the use of statin and angiotensin converting enzyme inhibitors (ACEI) in FDS type 2 patients increased from 10% to 52% and from 22% to 65%, respectively, over the 8-year follow-up period (unpublished observations).

### **The need for Phase II**

The clear implications from Phase I and other recent data are that i) the incidence of type 1 and type 2 diabetes is increasing rapidly, ii) glycaemic control is not improving despite growing evidence of the benefits of intensive blood glucose-lowering therapy, and iii) reductions in macrovascular complications reflect more

intensive cardiovascular management in the community. It is of direct relevance that the 33% 2-year mortality rate in conventionally treated diabetic patients after myocardial infarction in the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study carried out in the early 1990s<sup>31</sup> had fallen to 19% in similar patients in the more recent DIGAMI-2 Study<sup>32</sup> in the presence of increased use of aspirin, beta-blockers, ACEI and especially statin therapy. In addition, the low cardiovascular event rates relative to UKPDS and the non-significant primary endpoint effects in recent type 2 intervention trials such as Prospective Pioglitazone Clinical Trial in Macrovascular Events<sup>33</sup> and Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)<sup>34</sup> could also be explained, at least in part, by more intensive vascular risk factor management as part of usual care. There is, however, a pressing need for these management trends and their consequences found in the atypical setting of an intervention trial to be confirmed in community-based cohorts.

Such management changes have cost implications. Our Phase I cost data appear accurate<sup>35</sup> and, unlike a top-down costing approach, the patient-level design has allowed examination of many facets of care and provided detailed information for input into economic models and evaluations. Coupled with the wide range of variables encompassed by FDS (see below), we have been able to examine which groups are disadvantaged in terms of service delivery<sup>36</sup>, how expenditure in one area (e.g. medications) may be offset in another (e.g. inpatient care)<sup>37</sup>, and the cost-effectiveness of aspects of management such as SMBG<sup>20</sup>. The cost study within Phase II will provide detailed longer-term longitudinal cost data that track changes in epidemiology and management.

### **Potential benefits of Phase II**

The important short-term shifts in epidemiology and management of diabetes and their cost implications fully justify the proposed Phase II Study. Phase I data are available for comparison, facilities for new data collection and analysis are well established, and there is the opportunity to improve on and extend the successes of Phase I to cover a total follow-up of nearly two decades. AusDiab has also generated diabetes-specific data but from a sample of patients less than one-third the size of that of Phase I<sup>12</sup>. In fact, the FDS remains the largest diabetes cohort study undertaken in Australia and is one of the largest of such studies internationally.

*i. Consolidation and expansion* of Phase I findings relating to non-standard complications. In the case of reduced lung function, we would expand the 875 patient-years of follow-up and the range of explanatory variables measured to explore the underlying mechanisms we have postulated<sup>13</sup>. This should allow a robust assessment of links between lung damage and other consequences of hyperglycaemia including microangiopathy (especially peripheral and autonomic neuropathy), plasma AGEs and an increased susceptibility to respiratory infections. Our Phase I osteoporosis data were from a relatively small cross-sectional sub-group<sup>19</sup>. Longitudinal biochemical, densitometry and especially fracture data could strengthen our observation that male gender is a risk factor for osteoporosis and which could justify an intervention study. In addition, the recognised association between fractures and glitazone therapy<sup>38</sup>, and the increasing use of these drugs in type 2 diabetes management, provide further justification for this sub-study. We have observed that depressive symptoms predict all-cause and cardiac-related mortality in type 2 diabetes, mainly through the presence of complications<sup>34</sup>. Our depression assessment was from a subscale embedded in the General Health Status measure (one of the best available when the FDS was designed)<sup>39</sup> in Phase I and we plan to use contemporary validated instruments administered longitudinally and interpret<sup>40</sup>d in the light of use of modern antidepressant drug therapy in Phase II. The relationship between depressive symptomatology<sup>41</sup>, cognitive dysfunction and the effectiveness of diabetes self-management in older patients is a further area of interest and importance that would be facilitated by the proposed data collection in Phase II.

*ii. Towards an Australian diabetes-specific vascular risk calculator.* The development of such an instrument has become a recent priority as it could have a future role in guiding management including therapeutic requirement. We have assessed the validity of the UKPDS calculator<sup>42, 43</sup> and the selected nature of the UKPDS sample means that a local version is more appropriate<sup>44</sup>. The prototype has good discrimination, calibration (by Hosmer-Lemeshow  $\hat{C}$  test) and accuracy (by Brier score), but further validation is required to assess generalisability to the broader Australian diabetic population.

*iii. Expansion of health economic analyses.* We plan to broaden our cost assessment to nursing/ residential care, dental care and optometry. We will link our data with Silver Chain (community nursing), Ambulance and Emergency Department databases that were unavailable previously. In view of changes in diabetes diagnosis and treatment since the 1990s, it is important to repeat the Phase I cost study to ascertain how, what, where, why and in which sub-groups costs have changed and the consequences for outcome and quality-of-life. We will expand the estimation of direct non-health care costs to include home care and indirect costs to include disability. We will also assess intangible costs through loss of QoL as a result of diabetes by administration of a validated diabetes QoL questionnaire as well as a general health status instrument, the Short Form (SF)12. Through follow-up of nearly 900 survivors in the Phase I cohort, we will track changes over 20 years and provide valuable trend data on pharmaceutical, inpatient and nursing home costs in this group.

*iv. New initiatives.* There is growing evidence that novel biochemical vascular risk factors including inflammatory markers, adipokines, modulators of haemostasis, products of glucose-mediated tissue damage and indices of cardiac systolic/diastolic function could be important in the pathogenesis and prognosis of diabetic angiopathy and important clinical endpoints such as cardiac failure<sup>45-49</sup>. Most such evidence has, however, been collected from clinic- or trial-based patient samples. There is, therefore, a need for studies of hs-CRP, homocysteine, PAI-1, adiponectin, AGE and NT-proBNP in a community setting. It is of interest that the macrovascular benefits of statin and glitazone therapy involve a reduction in vascular inflammation<sup>50</sup>. Since observational studies provide estimates of treatment effects that are neither consistently larger than, nor qualitatively different from, those from randomised, controlled trials<sup>51</sup>, Phase II could provide valuable data on the effects of different cardiovascular and diabetes therapies on these variables.

## **RESEARCH PLAN**

### **Study sites**

Participants will primarily be assessed at FH, but children may choose to be assessed at the Endocrinology Department at Princess Margaret Hospital for Children (PMH) if they prefer. FH is the adult referral hospital for the study catchment area and PMH is the only tertiary referral hospital in WA for children <16 years of age. Both units have had extensive experience in epidemiological and intervention studies, and have well-developed clinical research facilities. This combination of sites should ensure as complete ascertainment, recruitment, data collection and patient retention as possible.

### **Study team**

We have assembled a team with extensive experience and an international standing in diabetes research. All aspects of the proposal are covered by existing expertise amongst the CIs and AIs, most of whom were involved in Phase I. CID joins Phase II to strengthen paediatric aspects and CIE will co-ordinate expanded health economic analyses. The AIs include an ophthalmologist with a special interest in diabetic retinopathy, a psychiatrist, a vascular surgeon, a geneticist and a dietitian who will assist in areas that proved to be of particular clinical/ epidemiological importance in Phase I or which were identified as needing additional expert input.

### **Study design, patient population and recruitment methods**

The observational study design of Phase I has been retained. Based on data from Australian Bureau of Statistics (ABS)<sup>52</sup>, AusDiab<sup>12</sup> and Juvenile Diabetes Research Foundation<sup>53</sup>, the Phase I catchment area will contain ~145,000 people in 2008 (a 15% increase from 1991), of whom 3,900 will have diabetes. Assuming the same case ascertainment (estimated to be 80%) and recruitment (63%) as Phase I, we anticipate that ~2,000 patients will enter Phase II. At the end of 2006, 882 (62%) of the Phase I cohort were alive, 689 of whom still lived in the study area (8 had moved interstate/overseas or were untraceable, but most of the other 185 lived in nearby suburbs). Thus, the Phase II cohort will comprise Phase I survivors and ~1,400 new recruits from the catchment area. Based on the distribution of patients in Phase I, ~90% would have clinically-diagnosed type 2 diabetes, with 5% of these showing serological/ phenotypic evidence of LADA<sup>10</sup>. Type 1 patients and a small number with secondary diabetes (<0.5%) would make up the remainder. Preliminary analyses of ABS data from 1991 and 2001<sup>52</sup> suggest that the proportion of SE patients may be

one-third lower than in Phase I but the larger total cohort should ensure valid assessment of differences between the two largest FDS ethnic groups (AC and SE).

Recruitment methods would be as used in FDS Phase I, namely i) FH and PMH inpatient/outpatient lists including allied health visits; ii) general practitioner (GP)/specialist referrals; iii) referral from diabetes educators, podiatrists, dietitians, community health nurses and Aboriginal health workers, iv) advertisements in state/local media, and in pharmacies, optometrists and shopping centres; v) relatives, friends and other diabetic contacts of recruited patients. We have just arranged a mail-out through Diabetes Australia in which all National Diabetes Supply Scheme (NDSS) registrants with a catchment area postcode and a willingness to participate in research were asked to contact FDS staff. As in Phase I,<sup>10</sup> we will attempt to gather as much data as possible from the non-recruited patients to allow an assessment of the representative nature of the Phase II cohort.

The recruitment of children will involve a more detailed referral (see Recruitment Flowchart, appendix 1). Eligible clients of PMH Diabetes team at Rockingham and Kwinana Hospital and PMH will be given a Parent Information Sheet and Child Information Sheet at their clinic visit and receive a brief explanation of the project. Eligible and willing clients will be asked if they are prepared to have their contact details shared with the research team (written consent will be taken for this - see Recruitment Form, appendix 2). A member of the research team will then contact the potential participants, discuss recruitment and organise a time for their initial assessments if they decide to be involved in the study. At their initial assessments, subjects will have to give written consent to participate in the study before assessment.

#### **Data collection schedule and techniques**

Consenting patients identified during a two-year registration period will be invited to an initial comprehensive assessment (Baseline) followed by similar face-to-face clinical/laboratory reviews every second year (Reviews 2, 4 etc.) interspersed with bi-annual postal/email/telephone assessments (Reviews 1, 3 etc.). In Phase I, annual follow-ups were performed but, in view of the relatively slow changes in clinical and laboratory variables of interest, alternate-year data collection seems appropriate. Of relevance is that, in the UKPDS, comprehensive assessments were performed 3-yearly. Although funding is requested for 5 years, it is anticipated (as was the case for Phase I) that additional funding will be obtained to sustain data collection beyond this time. Our aim would be to have data from Baseline and Reviews 1-6 for all available subjects, with study close-out at the end of 2015.

To improve the efficiency and completeness of data collection compared with that in Phase I, we will i) offer home assessments to patients unable to attend FH/PMH, ii) post/email questionnaires beforehand so that they can be completed in advance, iii) streamline assessments so that waiting times between components are minimised, iv) co-ordinate assessments with scheduled usual care appointments thus limiting the risk of duplication of data, v) offer out-of-hours timeslots for young, working patients, vi) continue the practice, successfully established in Phase I, of using relatives or hospital interpreters where English language fluency is likely to impair data collection (we also have Italian and Croatian-speaking staff members), vii) obtain contact details of people who could help with patient communication if this becomes difficult, and viii) liaise closely with Aboriginal health workers/Aboriginal Medical Services in the catchment area (as is being already done in an intervention study of glargine insulin) to improve identification, recruitment and retention of indigenous patients. We will attempt to collect all scheduled data from patients who move/have moved out of the study catchment area, including those who participated in Phase I but have since relocated (Phase I extension, Aim 2).

#### **Basic dataset to be collected (relevant to Aims 1 to 4)**

Selection of variables in Phase I was a compromise between research interest, relevance to clinical management, time constraints/patient inconvenience and available funding. To facilitate the proposed Phase I extension (Aim 1), the same variables will be collected but with increased data relating to diet, exercise, respiratory symptoms including snoring, osteoporosis, depression, and indirect costs of diabetes (Aims 2 and 4).

*i. Questionnaire:* This would be administered face-to-face every second year and updated data collected by post/email (with subsequent telephone/postal validation if required) in alternate years. As in Phase I, i)

relatives/friends would be encouraged to attend with the patient to translate and/or provide additional relevant information/validation and ii) data would be independently verified, where appropriate, through review of FH/PMH case notes, communication with GPs, specialists and allied health workers, and/or other sources. To save time at the assessment, the asterisked items will be posted out beforehand and responses checked before patients leave the assessment.

Where necessary – for example, details of medical information, family history of diseases questionnaire and pedigree<sup>54</sup> – the child's parent will answer questionnaires on behalf of his/her child.

1. *Demographic data:* Age; sex; place of residence (including nursing home and hostel); marital status; country of birth/parents' birth; language normally spoken at home; self-described ethnicity (ethnic background in Phase I was assessed principally from self-description, with other contributory variables including country of birth/parents' birth and language spoken at home<sup>10</sup>); English fluency; educational level; employment history; income bracket; GP details; health insurance status; health care card holder status; home support (carer, community nurse, meals on wheels); names, addresses and telephone numbers of two friends or relatives not living with the patient to facilitate patient communication, if required (appendix 3).
2. *Diabetes-specific data:* Diagnosis date/method including gestational diabetes in females; first symptoms; family history (appendix 3 continued); dietary/treatment history (including reasons for drug discontinuation, if known); blood glucose self-monitoring including duration and frequency; hypoglycaemia frequency, severity and unawareness; vascular and other complications; hospital admissions; frequency of GP/outpatient/specialist/allied health (diabetes education, dietetics, podiatry, optometry, dental) appointments (appendix 4).
3. *Current lifestyle measures:* A self-administered validated food frequency questionnaire from the Anti-Cancer Council of Victoria<sup>55</sup> will be used to assess nutrient intake from standard portion weights and nutrient composition<sup>56</sup> (appendix 5). Participants will self-report frequency/duration of physical activity during the previous week\* using the Active Australia Survey questionnaire which provides valid estimates of physical activity<sup>57</sup>. Sedentary behaviours will also be assessed specifically<sup>58</sup>. These tools will allow direct comparison of Phase II data with those of AusDiab<sup>59</sup> (appendix 6).
4. *Availability of care:* Access/transport to GP/clinic; need/provision of interpreter; domiciliary support; financial constraints on consultations, treatment, glycaemic monitoring (appendix 4).
5. *Knowledge of diabetes:* Sources (doctors, nurses/educators, dietitians, friends, others); 15-question validated multiple choice knowledge test as used in Phase I<sup>60,61</sup> (appendix 7).
6. *General medical information:* Past illnesses including pulmonary disease, depression, osteoporosis (including prior bone densitometry/fractures), dementia and dental history; other medications (including Pharmaceutical Benefits Scheme, private script, over-the-counter and complementary therapies) (appendix 4 and 8); smoking/alcohol; allergies; family history of diseases questionnaire and pedigree<sup>54</sup>(appendix 3); visual problems requiring optometrist review and glasses; sleep pattern (including snoring<sup>62</sup>) (appendix 9); in females, date of first and last menstrual period (appendix 4).
7. *Current health status:* SF-12<sup>63</sup> (appendix 10); Audit of Diabetes Dependent QoL (ADDQoL)<sup>64</sup> (appendix 11); PedsQL (Generic core scales and diabetes module for ages 5-17 years) (appendix 12-17).
8. *Cognitive function, mood and activities of daily living:* children 12 years of age and older will be assessed for depressive symptoms with the Center for Epidemiological Studies Depression Scale (CES-DC) (appendix 18)<sup>65</sup>; Big Five Inventory will be used to investigate personality traits in children 11 years and older (appendix 19)<sup>66</sup>and Spence Children's Anxiety GAD Subscale (attached).(appendix 20) will be administered to measure generalised anxiety in all the children.
9. *Costs of diabetes:* See table below. These will be determined as in Phase I from self-reported usage and linkage to WADLS, Ambulance, Emergency Department and Silver Chain databases.

ii. **Clinical examination** would be performed every second year and adapted for children according to age.

The full assessment includes the following (appendix 21):

1. Anthropometric measures: Height, weight, BMI; waist circumference, waist-hip ratio; body fat by bio-impedance.

2. Cardiovascular status: Supine/erect pulse rate and blood pressure; pulse rate changes on Valsalva manoeuvre, deep inspiration, 30:15 ratio; jugular venous pressure; presence/absence of carotid bruits; heart sounds; peripheral/sacral oedema; peripheral pulses/Doppler studies (for determination of ABI); foot care (including dry skin, callus, ulcer, deformity); 12-lead ECG.
3. Respiratory assessment: Pulse oximetry, auscultation of lung fields, spirometry (for children over 10 years of age).
4. Neurological assessment: Sensory testing of feet, including monofilament and biothesiometry, knee/ankle jerks to generate a Michigan Neuropathy Screening Instrument clinical score<sup>67</sup>.
5. Ophthalmic assessment: Visual acuity/fields (logMAR chart); fundus photography through undilated pupils (drops applied to dilate pupils with patient consent only if photographs are poor quality) using a Canon CR-DGI non-mydratic camera centred on optic disc and macula (standard fields 1 and 2) for grading using a modified Early Treatment of Diabetic Retinopathy Study scale at the Lions Eye Institute through AI Tim Isaacs<sup>68</sup>. Where there is an inadequate retinal view, data from recent external ophthalmic assessments will be accessed or specialist ophthalmic assessment arranged.

*iii. Laboratory tests* will be done every second year. Patients would attend after a >10-hour overnight fast. Venous blood and spot morning urine specimens will be collected and serum and EDTA plasma prepared from centrifuged blood. All standard-care assays (serum glucose, glycated haemoglobin (HbA1c), serum urea/electrolytes, serum cholesterol, triglycerides, HDL-cholesterol and non-HDL-cholesterol, serum uric acid, liver function, urine albumin and creatinine to provide the ratio (ACR) will be performed promptly in the laboratories of PathWest Laboratory Medicine WA, FH using the same assay methodology as for Phase I. In addition, each patient will have a full blood count, glutamic acid decarboxylase antibodies at baseline (to permit identification of patients with LADA<sup>10</sup>), plasma C-peptide, and serum insulin, the latter to allow calculation of beta cell function and tissue insulin sensitivity by Homoeostasis Model Assessment<sup>69</sup>. Aliquots of remaining serum, plasma, urine and EDTA whole blood will be stored at -80°C for further specialised analyses as appropriate.

#### **Specialised dataset to be collected (relevant to Aim 3)**

In a randomly-selected subset of 1000 patients (approximately 900 with type 2 and 100 with type 1 diabetes), additional data will be collected at baseline. These will comprise:

- i.* biochemical tests (serum hs-CRP, homocysteine, PAI-1, adiponectin and AGE as indicated above; markers of calcium metabolism and bone turnover and sex hormones<sup>19</sup>; serum thyrotropin, free thyroxine and thyroid antibodies<sup>70</sup>; and plasma NT-proBNP)
- ii.* vascular investigations using techniques already in use at FH (carotid Doppler studies for intimal media thickness; Sphygmocor® pulse waveform analysis, AtCor Medical, West Ryde, NSW)
- iii.* bone densitometry by dual-energy X-ray absorptiometry (Hologic, Bedford, MA, USA)<sup>19</sup>

#### **Data validation and accuracy**

Measures to reduce recruitment bias are as under *Data collection schedule and techniques* above. Recall bias, obtrusive measures, response sets and misclassification are minimised by i) staff training in interview skills, ii) attendance of relatives/friends familiar with the patient, iii) validation of responses within and across assessments, iv) validation from other sources which, especially for key endpoints such as cardiovascular disease, heart failure, stroke, blindness and renal failure, includes scrutiny of individual hospital records. Self-reported medical problems are checked against examination and laboratory data. Computer routines identifying outliers are run regularly. Data in all reports issued to GPs/specialists after each patient visit are scrutinised and signed off by the CIs.

#### **Data linkage**

Phase II data will be supplemented (as in Phase I) by the WADLS<sup>8</sup> which, with participant consent, will provide data for both public and private hospitalisations, ambulance, emergency department and Silver Chain use from one year before study entry to the end of follow-up, as well as mortality data. We will also request consent for linkage with the National Death Index in case participants move interstate. We will obtain

consent from the patients for de-identified linkage with the Commonwealth Aged Care and PBS/MBS databases but, as this information will be already sought at Phase II assessments, this may represent a validation exercise.

### **Data analysis**

*i. Cross-sectional and longitudinal statistical analysis.* For all identified subjects, basic variables (e.g. age, sex, diabetes type) will be compared between recruited and non-recruited subjects to ascertain the representativeness of the recruited cohort. Multiple linear and logistic regression analyses using SPSS for Windows (version 16.0; SPSS, Inc., Chicago, IL) and SAS for Windows (Version 8.02; SAS Institute, Cary, NC) will be performed to identify which baseline variables are associated with prevalent diabetic complications, QoL, and diabetes-attributable costs accrued in the year before study entry.

During the follow-up phase, outcomes such as the development and progression of individual complications will be assessed by type of diabetes (type 1, type 2 and LADA). Cox proportional hazards modelling will be used to identify independent baseline predictors of the development and progression of endpoints. Multiple linear regression will also be used to identify which baseline variables predict i) changes in QoL and ii) the economic costs due to diabetes accrued between baseline and bi-annual reviews. Repeated measurements on patients will be accommodated using mixed linear regression models for quantitative factors and Generalised Estimating Equations (GEE) for binary or multinomial variables.

*ii. Economic analysis.* For resource cost-estimation (health and personal care) every resource will be allocated a cost estimate as outlined in the table below. Each cost will be attributed to i) government, ii) the health insurance provider, iii) the patient or iv) the carer. In the case of indirect costs, the cost of lost productivity due to time off work by patient and/or carer due to diabetes will be estimated using ABS data (Average Weekly Earnings/ Employee Earnings and Hours).

Cost component	Data source	Source of unit cost data
<i>Direct health care</i>		
Hospital inpatient	WA Data Linkage System	Casemix approach based on Diagnostic Related Groups; WA cost-weights
Hospital outpatient	Questionnaire; Emergency Department database linkage	Hospital accounting department data
Out-of-hospital medical services	Questionnaire; Ambulance database linkage	Medicare Benefits Schedule; Ambulance database
Dental, optometry and allied health services	Questionnaire	Appropriate professional bodies
Medications	Questionnaire	Schedule of Pharmaceutical Benefits; MIMS
Diabetes consumables	Questionnaire	Schedule of Pharmaceutical Benefits; NDSS 2000; Member prices of Diabetes Australia WA
Residential aged care	Questionnaire	Appropriate service provider
<i>Direct non-health care</i>		
Travel to/from services	Questionnaire	Transperth; Australian Taxation Office
Home care	Questionnaire; Silver Chain linkage	Appropriate service provider (eg Silver Chain, Meals-on-Wheels)
<i>Indirect costs</i>		
Lost productivity (patient and informal carer) and lost income	Questionnaire	ABS (Average Weekly Earnings/ Employee Earnings and Hours)
Disability	Questionnaire; physical assessment	
<i>Intangible costs</i>		
Quality of life	Questionnaire	

*iii. Study power:* We aim to recruit 2000 subjects (200 with type 1 and 1800 with type 2 diabetes). Over 6 years of follow-up, Phase I data suggest that 18% of type 2 and 7% type 1 diabetic subjects will die, although recent improvements in cardiovascular risk management may reduce these proportions. A minority of participants is expected to move overseas or interstate and thus no longer be captured by the WA mortality

register or hospital morbidity database<sup>6</sup>. Thus, for hard endpoints (death or hospitalisation), there will be of the order of 1440 (80%) type 2 and 180 (90%) type 1 participants with complete follow-up data at the end of 6 years. For type 2 diabetes, there will be sufficient numbers to detect small effect sizes<sup>53</sup> (e.g. a frequency difference of 10%, a relative risk of 1.2 or an odds ratio of 1.5) and for type 1 diabetes, there will be sufficient numbers to detect small-moderate effect sizes<sup>53</sup> (e.g. a frequency difference of 20%, a relative risk of 1.5 or an odds ratio of 2.5) with 80% power and a significance level of 0.05.

In relation to power considerations for sub-group analyses (Aim 3), we have looked at hs-CRP as an exemplar. In a recent study of hs-CRP and coronary heart disease (CHD) in type 2 patients<sup>71</sup> in which the coronary death rate was 2.1%/year, the highest hs-CRP tertile was independently associated with an increased risk of coronary mortality of 1.7 times compared with the lowest two tertiles. In Phase I the cardiovascular event rate (death or hospitalization from/with myocardial infarction or stroke or sudden death) was 3.0%/yr. Since we are hypothesizing that rates have fallen since then, 2.0%/year has been assumed for the Phase II sub-group. For the random sample of 1000 diabetic patients, a hazard ratio of 1.26 between the highest tertile and lowest two tertiles will be detectable with 80% power and a significance level of 0.05. Since the other variables to be collected in this group show similar differences, we anticipate adequate power for most of these analyses.

## TIMELINES

The compression of the registration period from the 3 years in Phase I to 2 years will allow all baseline assessments to be carried out before the next full reviews are scheduled. It is planned to assess 1,000 patients in Years 1 and 2, representing 4 patients per working day. We estimate that each full assessment will take 3 hours with optimised scheduling of procedures. During Year 2, the postal/email/telephone assessments will begin. In Years 3 and 4, the first full clinical/biochemical reviews will start. We have estimated, based on Phase I attrition rates with an adjustment for improved retention in Phase II the workload by year as follows:

	Year 1	Year 2
Clinical/biochemical assessment	1000	1000
Postal/email/telephone assessments	-	935
Total	1000	1,935

## OUTCOMES AND SIGNIFICANCE

Regarding the four National Research Priorities, the present application addresses *ageing well*, *ageing productively* within Promoting and Maintaining Good Health. It is also directly relevant to Goals 2 (to improve health related quality of life, and reduce complications and premature mortality in people with type 1 and type 2 diabetes), 5 (to advance knowledge and understanding about the prevention, cure, and care of diabetes through a comprehensive research effort), and 6 (to improve the capacity of the health system to deliver, manage and monitor services for the prevention of diabetes and the care of people with diabetes) of the National Diabetes Strategy and Implementation Plan.

As evidenced by the productivity of the original study, FDS Phase II would be expected to continue to provide valuable demographic, socioeconomic, clinical and health-economic data relating to the natural history of both type 1 and 2 diabetes, and LADA. There is the opportunity to: i) Build on the findings of Phase I in respect to the development of conventional and non-standard complications, and to explore whether changes in their prevalence and severity reflects contemporaneous changes in diabetes management since the early 1990s. ii) Extend the focus on the effects of diabetes on QoL, mood, cognition and ADL; these aspects were, in part because of the lack of validated measurement tools when the original FDS was planned, not the primary focus of Phase I but which have proved to be interesting facets of the impact of diabetes on the individual and of direct relevance to management. iii) Track costs as an extension of Phase I findings which suggest that factors such as cardiovascular pharmacotherapy and length of inpatient stay are changing significantly in the short term. iv) Examine, in a community setting, the potential of novel biochemical vascular risk markers such as hs-CRP and adiponectin in a situation of sufficient patient numbers and characterisation of other important confounding explanatory variables.



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