ADVANCE

Action in Diabetes and Vascular Disease

Preterax and Diamicron MR Controlled Evaluation

A factorial randomised trial of blood pressure lowering with a fixed low-dose perindopril-indapamide combination and intensive glucose control with a modified-release gliclazide-based regimen for the prevention of vascular disease among high risk individuals with type 2 diabetes

Study Protocol

(International Protocol Amendment 1 dated 30 November 2005)

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ADVANCE Study Summary Sheet

Name of Sponsors: *The George Institute for International Health* University of Sydney PO Box M201, Missenden Road Camperdown Sydney, NSW 2050, Australia *Institut de Recherches Internationales Servier* 6 Place des Pléiades 92415 Courbevoie, cedex, France	**Individual Study Table referring to Part of the Dossier**	***(for National Authority use only)***
Name of Finished Product: ***Preterax® (Predonium®) and Diamicron MR®***	**Volume:**	
Name of Active Ingredient: ***Fixed low-dose perindopril 2mg/indapamide 0.625mg*** ***Modified release gliclazide 30 mg***	**Page: 1/2**	

Title of Study:
ADVANCE: *Action in Diabetes and Vascular Disease*: Preterax and Diamicron MR Controlled Evaluation

A factorial randomised trial of blood pressure lowering with a fixed low-dose perindopril-indapamide combination and intensive glucose control with a modified-release gliclazide-based regimen for the prevention of vascular disease among high risk individuals with type 2 diabetes

Main Coordinators:
Prof S. MacMahon, University of Sydney, Australia
Prof J. Chalmers, University of Sydney, Australia

Study Centers:
The study will recruit participants from about 200 clinical centres in several countries in Australasia, Asia, Europe and North America.

Study Period (years): Feb 2001 to Dec 2007 or at such time that the Management Committee, on the recommendation of the Data & Safety Monitoring Committee, recommend completion of participant treatment and follow-up.	**Phase of Development:** Phase III **Duration:** 5-6 years

Objectives:
To determine the effects of a fixed low-dose perindopril-indapamide combination (2mg/0.625mg) vs placebo and a modified-release gliclazide (30-120mg)-based intensive glucose lowering regimen vs standard guidelines-based therapy on major macrovascular and microvascular complications among individuals with type 2 diabetes over a scheduled mean treatment period of 5.5 -6 years. Secondary outcomes include other major events, cognitive function and quality of life. An economic analysis will also be conducted.

Methodology:
The study is a factorial, multicentre, international, randomized controlled trial. The comparison of fixed low-dose perindopril-indapamide combination vs placebo will be double-blind and the comparison of the modified-release gliclazide-based intensive glucose lowering regimen vs standard guidelines based therapy will be open. There will be a 6 week run-in period on perindopril-indapamide combination (2mg/0.625mg) before randomisation. At randomisation, participants will be randomised to receive one of four treatment combinations for a scheduled mean period of treatment of 5.5 - 6 years: fixed low-dose perindopril-indapamide combination plus modified-release gliclazide-based intensive glucose lowering regimen, fixed low-dose perindopril-indapamide combination plus standard guidelines-based glucose lowering, placebo plus modified-release gliclazide-based intensive glucose lowering regimen, or placebo plus standard guidelines-based glucose lowering.

Planned number of participants:
- Total: 10 000
- Fixed low dose perindopril-indapamide plus modified-release gliclazide-based intensive glucose lowering regimen: 2500
- Fixed low dose perindopril-indapamide plus standard guidelines-based glucose lowering therapy: 2500
- Placebo plus modified-release gliclazide-based intensive glucose lowering regimen: 2500
- Placebo plus standard guidelines-based glucose lowering therapy: 2500

Diagnosis and main criteria for inclusion:
- Age 55 years old or over with type 2 diabetes (diagnosis of diabetes made at age 30 years or older, and no requirement for regular insulin therapy).
- A substantially elevated risk of cardiovascular disease, indicated by: a history of major macrovascular or microvascular disease, a first diagnosis of type 2 diabetes made 10 or more years prior to entry, age 65 years or over or other defined major risk factor for vascular disease.
- Informed signed consent.
- No definite and specific contraindication or indication for any of the study treatments.

Test medication
- Fixed low-dose perindopril-indapamide (2 mg/0.625 mg) combination: 1 tablet daily for the first 3 months and 2 tablets daily thereafter unless there is a specific contraindication to the increased dose. Medication taken orally in the morning unless otherwise indicated.
- Modified-release gliclazide (30-120mg; 1-4 tablets)-based intensive glucose lowering regimen: gliclazide MR taken orally in the morning unless otherwise indicated. Other treatment as required to achieve target haemoglobin A_{1C} level (<6.5%).

Reference drug:
- Matching placebo for the fixed low dose perindopril-indapamide (2 mg/0.625 mg) combination: administered in an identical dosing schedule.
- Standard guidelines-based glucose lowering (usual care).

Duration of treatment:
Mean 5.5 - 6 years

Statistical methods
The principal analyses of the effects of treatment on primary study outcomes will involve Cox models. The analyses of all major efficacy and safety outcomes will include all randomised participants. Analyses of other dichotomous, categorical and continuous data will be conducted using standard statistical tests.

ADVANCE Study Summary Sheet (continued)

Name of Sponsors: *The George Institute for International Health* University of Sydney PO Box M201, Missenden Road, Camperdown Sydney, NSW 2050, Australia *Institut de Recherches Internationales Servier* 6 Place des Pléiades 92415 Courbevoie, cedex, France	**Individual Study Table referring to Part of the Dossier**	***(for National Authority use only)***
Name of Finished Product: ***Preterax® (Predonium®) and Diamicron® MR***	**Volume:**	
Name of Active Ingredient: ***Fixed low-dose perindopril 2mg/indapamide 0.625mg*** ***Modified-release gliclazide 30 mg***	**Page: 2/2**	

Contractual signatories

I confirm that I have read the entire protocol and the "Information for and consent of participants" document attached to the protocol.	**Name**	**Date**	**Signature**
Investigator			
The George Institute for International Health, University of Sydney			
Institut de Recherches Internationales Servier			

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1. ETHICS AND CONFIDENTIALITY

Approvals from institutional ethics committees and other regional or national regulatory bodies will be obtained prior to the initiation of the study in any centre. The study will be conducted in accordance with the principles set out in the Declaration of Helsinki and its subsequent amendments of Tokyo, Venice, Hong Kong and Somerset West and written informed consent, complying with both these principles and local, regional and national requirements will be obtained from all participants prior to entry into the study. The study will not commence in any centre until all the necessary documentation has been completed.

In obtaining informed consent, the study investigator will provide the potential participant with information about the purposes, methods, possible risks and benefits of participating in the study. The consent obtained will include consent for collection and storage of blood samples for extraction of DNA and analyses of the association between genetic polymorphisms, treatment effects and disease risks. The consent form will indicate that no individual results from DNA analyses will be made available to participants or any other party. All potential participants will have an opportunity to discuss the study with study staff. The participants and the person obtaining informed consent will each sign and date two copies of the consent form, one copy of which will be provided to the participant and the other copy of which will be stored in the participants case record folder. Participation in the study will be voluntary and all participants will be free to withdraw at any time, without consequence for their future care. For participants that are not able to read or sign the participant information sheet or consent form, a legal representative or other person approved by the relevant regulatory authorities may do so on their behalf.

Modifications to the protocol, participant information sheet or consent form will be submitted to the ethics committee for approval and appended to this document. Such modifications will only be implemented once ethics committee approval has been obtained, unless an amendment is being made to eliminate immediate hazards to study participants.

All data generated by the study will remain strictly confidential and no report will contain any information that would allow an individual participant in the study to be identified. However, in order to facilitate complete data collection and long-term follow-up individual contact details will be collected at registration and stored at the Local Clinical Centre. These details will be stored separate from other data and will not be transmitted to the Data Management Centre. Participant records transmitted to the Data Management Centre will be identified only by a unique registration/randomisation number, the participants' date of birth and the participants' initials.

2. ADMINISTRATIVE STRUCTURE

This investigator-initiated study is co-sponsored by The George Institute for International Health, University of Sydney and the Institut de Recherches Internationales Servier. The study Management Committee, which includes no employees of Servier, is responsible for overseeing all aspects of the conduct of the trial and will be responsible for the preparation and publication of the principal results of the study, independent of Servier. A Liaison Committee involving the study co-principal investigators and representatives of Servier has been established to facilitate communication between the Management Committee and Servier.

The study will be conducted in about 200 clinical centres (Local Clinical Centres) from Australasia, Asia, Europe and North America. International coordination will be provided by The George Institute for International Health in Sydney, Australia (International Coordinating Centre) and central data management will be provided by the Clinical Trials Research Unit in Auckland, New Zealand (International Data Management Centre). Regional coordination will be provided by five centres (Regional Coordinating Centres) located in Melbourne (for Australasia and South East Asia), Beijing (for China), London (for the UK, Ireland, Estonia, Lithuania and Russia), Utrecht (for other participating countries in Continental Europe) and Montreal (for Canada).

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3. INTRODUCTION

3.1 PREVALENCE OF TYPE 2 DIABETES MELLITUS

Diabetes mellitus is a major global health problem. The World Health Organization estimated that in 1995 there were about 135 million adults with diabetes world wide.[1] The prevalence of type 2 diabetes among individuals aged 30 to 64 years ranged from just a few percent in rural areas of China and Africa to more than 10% in some Hispanic, African American, Middle Eastern and Pacific Islands' populations.[1, 2] The countries with the largest numbers of diabetics are India (19 million), China (16 million) and the USA (14 million).[1] In many developing countries, a sharp increase in the prevalence of type 2 diabetes is likely given the increasing mean population age together with evidence of large numbers with impaired glucose tolerance (e.g. in some areas of India, the prevalence of impaired glucose tolerance is twice that of type 2 diabetes). By 2025, it is projected that the total number of individuals with diabetes will rise to about 300 million, with particularly large increases likely in Asia.[1]

3.2 VASCULAR COMPLICATIONS OF TYPE 2 DIABETES MELLITUS

3.2.1 Macrovascular Disease

Type 2 diabetes increases the risks of several types of macrovascular disease. In Western populations, coronary heart disease (CHD) is the most common cause of death in individuals with type 2 diabetes, among whom the risk of death from this cause is increased approximately three-fold.[3] The risk of non-fatal myocardial infarction is similarly increased[4, 5] as are the risks of ischaemic stroke[6] and congestive heart failure.[7, 8] The consequences of type 2 diabetes in other populations are less certain, but new analyses from the Asia Pacific Cohort Studies Collaboration[a] involving more than 160,000 individuals followed for an average of 7 years demonstrate highly significant 2-3 fold increases in the risks of nonfatal myocardial infarction or death from CHD, stroke, renal disease, death from any cardiovascular cause and total mortality in individuals with diabetes (mostly type 2) from populations throughout the Western Pacific region. Data from this project indicate that stroke, rather than coronary heart disease, was the most common cause of death among individuals with diabetes in populations from East and South East Asia.

3.2.2 Microvascular Disease

The risks of several microvascular diseases are also increased among individuals with type 2 diabetes. Retinopathy is common even among patients newly diagnosed with type 2 diabetes: at entry to the United Kingdom Prospective Diabetes Study (UKPDS) more than one-third of participants had evidence of retinopathy, which was advanced in about 5%.[9] In the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) after 10 years follow-up, there was evidence of some degree of retinopathy in more than two-thirds of type 2 diabetic patients: proliferative retinopathy was observed in 10% of those on oral treatment and 24% of those on insulin.[10] In Western populations, diabetic retinopathy is the most common cause of blindness among individuals under the age of 60 years.[10] Nephropathy is another common microvascular complication of type 2 diabetes. In various studies, 14-19% of patients newly diagnosed with type 2 diabetes had microalbuminuria and 2-5% had macroalbuminuria.[11-13] In long-term studies, the cumulative incidence of nephropathy (e.g. >300 mg/24 hr urinary albumin excretion) 20 years after diagnosis ranged from 27-50%,[14, 15] while the incidence of end-stage renal failure (e.g. GFR <15 ml/min) 10 years after the development of proteinuria ranged from 10-35%.[16, 17] In most Western populations, diabetes is the leading cause of end stage renal failure and although the relative contributions of type 1 and type 2 diabetes vary, most studies suggest that at least half of all diabetic renal failure is due to type 2 diabetes.[14, 16, 18] Neuropathy is also frequent among patients with type 2 diabetes. In the Rochester Diabetic Neuropathy Study, about 60% of patients had some form of neuropathy that was symptomatic in about a third.[19] Lower

[a] Unpublished data, Asia Pacific Cohort Studies Collaboration. (Institute for International Health, University of Sydney)

extremity amputation is a serious complication of neuropathy and associated vascular changes in type 2 diabetes: in the WESDR after 14 years of follow-up, the cumulative incidence of lower-extremity amputation was about 10% in type 2 diabetic patients.[20]

3.3 RISK FACTORS FOR VASCULAR DISEASE IN TYPE 2 DIABETES MELLITUS

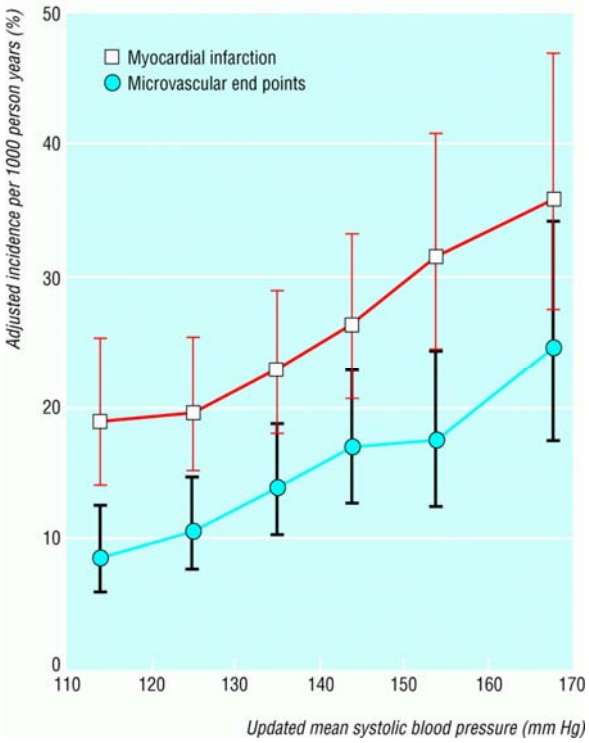
3.3.1 Blood Pressure

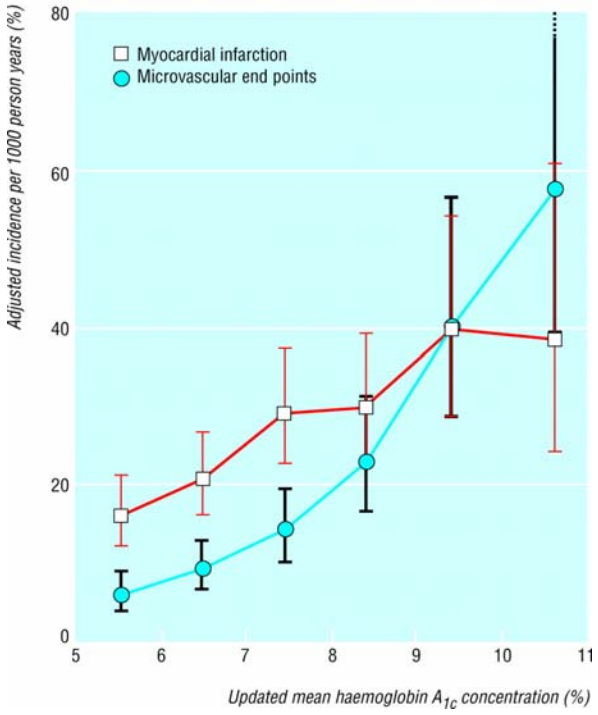
Blood pressure appears to be a particularly important determinant of the risks of both stroke and CHD among patients with type 2 diabetes.[3, 5] A large proportion of patients with type 2 diabetes are hypertensive[21, 22] and the associations of blood pressure with both stroke and CHD are continuous, with no lower level of blood pressure identified below which the risks do not continue to decline. In the Asia Pacific Cohort Studies Collaboration, the associations of systolic blood pressure with the risks of stroke and coronary heart disease were of similar strength among individuals with diabetes and those without diabetes. Among individuals aged 60-69 years at entry, the risk of death from stroke and major coronary events increased by 37% (SE 6) and 27% (SE 8), respectively, with every 10 mmHg increment in usual systolic blood pressure. In the Prospective Studies Collaboration, an age-dependent association of systolic blood pressure with death ascribed to diabetes was observed (personal communication: S. Lewington, University of Oxford): at age 40-59 years, the risk of death from diabetes increased by about two-thirds with every 10 mmHg increment in systolic blood pressure, whereas, at age 70-79 years the same increment in blood pressure was associated with about a one third increase in the risk of death from diabetes. In the UKPDS, usual levels of systolic blood pressure were also observed to be directly associated with the risks of myocardial infarction, as well the risks of microvascular disease in patients with type 2 diabetes[23] (Figure 1). Additionally, blood pressure levels have been shown to be directly associated with the risk of nephropathy in patients with type 2 diabetes,[24] with the rate of decline in glomerular filtration rate being 2-3 times higher in patients with hypertension.[25] Similarly, blood pressure levels have been observed to be directly associated with the risks of retinopathy[26, 27] and sensory neuropathy.[28]

3.3.2 Glucose Control

The level of glycaemic control among patients with type 2 diabetes also appears to be an important determinant of the risks of macrovascular disease. In the UKPDS, there was a 14% (95% CI 8 to 21%) decrease in the risk of myocardial infarction for every 1% decrease in mean levels of haemoglobin A_1c measured during follow-up (Figure 1).[29] Similarly, in the WESDR, there was a 10% (95% CI 4 to 17%) decrease in the risk of death from CHD and a 17% (95% CI 5 to 30%) decrease in the risk of mortality from stoke for every 1% decrease in the baseline level of haemoglobin A_1c.[10] Several other studies have reported similar continuous associations between the level of haemoglobin A_1c or fasting blood glucose and the risks of major coronary events.[30-33] The level of glycaemic control also appears to be an important determinant of the risks of microvascular disease. In the UKPDS, there was a 37% (95% CI 33 to 41%) decrease in the risk of microvascular complications for every 1% decrease in mean levels of haemoglobin A_1c measured during follow-up (Figure 1).[29] In the WESDR, the risks of retinopathy, nephropathy, neuropathy and lower extremity amputation all decreased in direct proportion to the level of haemoglobin A_1c among individuals with type 2 diabetes.[10] Similar findings have been reported from a number of other studies.[12, 28, 34]

Figure 1 Association of mean follow-up levels of systolic blood pressure and haemoglobin A_{1c} with the incidence of myocardial infarction and microvascular end points among 3642 individuals with type 2 diabetes (the United Kingdom Prospective Diabetes Study). Age, sex and ethnicity-adjusted incidence and 95% Confidence Intervals are shown.[23,29]





3.4 PREVENTION OF VASCULAR DISEASES IN TYPE 2 DIABETES MELLITUS

3.4.1 Blood Pressure Lowering Drugs

Data on outcome among hypertensive patients with type 2 diabetes have been reported from several randomised-controlled trials of blood pressure lowering drugs. In a meta-analysis of individual participant data from three trials of diuretic- or beta blocker-based therapy,[35] the proportional effects of treatment on the risks of major cardiovascular events among patients with diabetes were similar to those among patients without diabetes. In the 2,162 diabetic hypertensive patients in these trials, there were reductions of 36% in the risk of stroke (95% CI 10 to 55%) and of 20% in the risk of any major cardiovascular event (95% CI 2 to 34%), but there was no clear reduction in the risk of coronary heart disease (95% CI –11 to 55%).[35] Similar effects of a calcium antagonist-based blood pressure lowering regimen were observed in the Systolic Hypertension in Europe (SYST-EUR) trial.[36] These results are also consistent with the outcome of trials comparing more or less intensive blood pressure lowering therapy. In the UKPDS[37] and the Hypertension Optimal Treatment (HOT) study,[38] a lower incidence of stroke and of total major cardiovascular events was observed among diabetic patients assigned to more intensive blood pressure control (with regimens based on beta-blockers or ACE inhibitors in UKPDS and on a calcium antagonist in HOT). In the hypertensive arm of the ABCD trial, there were fewer deaths overall among individuals assigned more intensive blood pressure control, but there were no clear effects on cause-specific vascular outcomes (which were few).[39] Overall, the results of these trials are consistent in suggesting that a net blood pressure reduction of about 10 mmHg systolic among patients with hypertension and diabetes results in a reduction in stroke risk of about 35-40% and a reduction in total major cardiovascular events of about 20%. Most recently, the Heart Outcomes Prevention Evaluation (HOPE) Study demonstrated that prolonged treatment with the ACE inhibitor, ramipril, lowered systolic blood pressure by only 3 mmHg, and yet reduced stroke risk by a third

and coronary events by a fifth among high-risk diabetic patients, most of whom had a history of coronary heart disease. [40] The proportional effects of treatment appeared to be similar in diabetic and non-diabetic patients and in hypertensive and non-hypertensive patients.

The effect of blood pressure lowering on microvascular complications was investigated in the UKPDS: among patients assigned more intensive therapy, there was a 37% reduction in microvascular events mostly the need for retinal photocoagulation.[37] The HOPE Study also reported a reduction of about one-sixth in microvascular complications of diabetes, including nephropathy and retinopathy. Other smaller trials of ACE inhibitor-based regimens have shown similar effects on renal outcomes among hypertensive and non-hypertensive patients with type 2 diabetes.[41-43]

3.4.2 Glucose Lowering Therapy

Several small randomised trials, together with the larger Diabetes Control and Complications Trial (DCCT)[44-47], have investigated the effects of intensive glycaemic control in patients with type 1 diabetes. A meta-analysis of 16 of these trials demonstrated reductions of about one quarter in the risks of microvascular disease among those assigned intensive therapy, with separately significant reductions in retinopathy, nephropathy and neuropathy.[48] Another meta-analysis of 6 trials showed no clear reduction in the number of patients developing macrovascular disease (95% CI –17 to 56%).[49] Fewer trials have investigated the effects of intensive glycaemic control on vascular outcomes among patients with type 2 diabetes. A few small studies have reported reductions in microvascular disease among type 2 patients assigned intensive therapy.[50-52] The larger UKPDS demonstrated that lowering haemoglobin A1c by an average of about 1% with sulphonylurea- or insulin-based therapy reduced microvascular complications (mainly retinopathy requiring photocoagulation) by one-quarter (95% CI 7 to 40%).[53] There was a borderline-significant trend towards a reduced risk of myocardial infarction (95% CI 0 to 29%), but no clear reduction in stroke (95% CI –51 to 19%) or in diabetes-related deaths (95% CI –11 to 27%). However, the study had limited power to detect moderate, though potentially worthwhile, effects of glucose lowering therapy on macrovascular events (eg. a one-sixth reduction in events). Thus while the UKPDS did not provide convincing evidence of benefits for macrovascular disease, the results do not exclude the possible existence of worthwhile benefits.

3.5 UNRESOLVED ISSUES IN THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS

3.5.1 Blood Pressure Lowering Drugs

The available evidence suggests that blood pressure lowering drugs have great potential to reduce the risks of both microvascular disease and macrovascular disease among patients with diabetes. While most trials have been conducted in hypertensive patients alone, the results of HOPE suggest that there may be similar benefits of ACE inhibitors for non-hypertensive individuals. The degree to which the benefits of ACE inhibitors reflect reductions in blood pressure is somewhat uncertain, although the reductions in blood pressure among patients assigned ramipril in HOPE were apparently small. Nevertheless, there is still a strong case for expecting additional benefits to accrue from more intensive efforts to lower blood pressure in non-hypertensive as well as hypertensive patients with type 2 diabetes. This is suggested by the results of a recent overview of trials suggesting that more intensive therapy (targeting lower blood pressure levels within the normotensive range) conferred larger benefits on stroke and coronary heart disease than did less intensive therapy.[54] It is also consistent with evidence from epidemiological studies showing a continuous association of major macrovascular events with blood pressure levels across the entire range of usual blood pressure values. The present study therefore involves a randomised comparison of more intensive blood pressure lowering therapy using a fixed low-dose ACE inhibitor (perindopril) and diuretic (indapamide) combination versus placebo against a background of standard care that may include other antihypertensive therapy and ACE inhibitor therapy (with open-label perindopril) in high-risk hypertensive or non-hypertensive patients with type 2 diabetes. The fixed low-dose ACE inhibitor-diuretic combination was selected for two main reasons: first, the combination produces larger effects on blood pressure than does monotherapy with either agent;[55] and second, both classes of agents have been shown to confer benefits for vascular disease in placebo-controlled trials in several different patient populations. In addition, fixed-dose combination therapy with low doses of the individual agents minimizes dose-dependent side effects and

enhances adherence to treatment.[56] In this regard, the fixed low-dose combination of perindopril 2mg and indapamide 0.625 mg in doses of either one or two tablets daily has been demonstrated to be well tolerated and to produce sustained blood pressure reduction in studies of up to 12 months duration, among hypertensive patients.[57]

3.5.2 Glucose Lowering Therapy

The available evidence suggests that treatments for glycaemic control have an important role to play in the prevention of microvascular disease among patients with type 2 diabetes, although benefits for macrovascular disease have not been demonstrated convincingly. The results of the UKPDS neither confirm nor exclude reliably the existence of moderate, potentially worthwhile effects of glucose lowering on such outcomes. This has resulted in widespread clinical uncertainty about the net benefits conferred by glucose lowering treatments. There is also uncertainty as to whether very intensive glucose control regimens, targeting even lower levels of haemoglobin A_1c, will confer greater protection against either microvascular or macrovascular disease. The present study therefore involves a randomised comparison of very intensive sulphonylurea-based therapy versus standard guideline-based glucose control therapy in high-risk patients with type 2 diabetes. The aim of the intensive regimen is to reduce haemoglobin A_1c to 6.5% or lower (compared with haemoglobin A_1c targets of 7-8% suggested by most regional guidelines). The intensive glucose control regimen will be based on a modified-release formulation of a sulphonylurea, gliclazide MR (Diamicron MR), that provides 24-hour glucose control in a once a day dose. Sulphonylureas are effective, widely prescribed agents for the control of blood glucose levels among individuals with diabetes.[58] Gliclazide MR was selected for this study for the ease of administration and improved adherence associated with a once daily dosing schedule.[59] The glucose control and side effect profile associated with the use of gliclazide MR appear to compare favorably with other similar agents.[60]

3.6 SUMMARY

The present study is designed to determine whether benefits of more intensive blood pressure lowering with a fixed low-dose combination of an ACE inhibitor (perindopril) and a diuretic (indapamide) extend to both hypertensive and non-hypertensive individuals at high risk of cardiovascular events. The study will also determine whether there are moderate but worthwhile effects of a very intensive gliclazide MR-based glucose control regimen compared with standard guidelines-based therapy for glycaemic control. The effects of the two study interventions will be investigated simultaneously in a full 2 x 2 factorial design: this design will enable the study to determine the independent and additive effects of more intensive blood pressure lowering and more intensive glucose lowering for the prevention of both macrovascular and microvascular disease. The results should have important implications for decisions about the management of the rapidly expanding population of high-risk patients with type 2 diabetes.

4. OBJECTIVES

4.1 MAIN OBJECTIVES

The main objectives of this study are to investigate the effects of blood pressure lowering with a perindopril-indapamide combination and intensive glucose lowering with a gliclazide MR-based regimen on major macrovascular and microvascular disease events among high-risk, hypertensive or non-hypertensive individuals with type 2 diabetes.

4.2 SPECIFIC PRIMARY HYPOTHESES

4.2.1 Blood pressure lowering

- Participants randomised to receive the perindopril-indapamide combination will experience a lower incidence of the composite outcome of stroke, myocardial infarction or cardiovascular death than those assigned placebo.

- Participants randomised to receive the perindopril-indapamide combination will experience a lower incidence of the composite outcome of new or worsening nephropathy or microvascular eye disease than those assigned placebo.

4.2.2 Glucose control

- Participants randomised to receive gliclazide MR-based intensive therapy will experience a lower incidence of the composite outcome of stroke, myocardial infarction or cardiovascular death than those assigned standard guidelines-based glucose control.

- Participants randomised to receive gliclazide MR-based intensive therapy will experience a lower incidence of the composite outcome of new or worsening nephropathy or microvascular eye disease than those assigned standard guidelines-based glucose control.

5. STUDY DESIGN

5.1 SUMMARY

The study is a factorial randomised, controlled trial investigating the effects of a blood pressure lowering regimen and a glucose lowering regimen on the risks of serious vascular complications among individuals with type 2 diabetes. The overall design is illustrated in Figure 2 and 3. Following a 6-week run-in period on open fixed low-dose perindopril-indapamide (2.0mg/0.625mg) and usual glucose lowering treatment, eligible participants are randomly assigned to the two treatment comparisons:

- a double blind comparison of the perindopril-indapamide combination versus placebo and;
- an open comparison of intensive gliclazide MR-based therapy (target haemoglobin A1c <6.5%) versus the standard guidelines-based glucose lowering regimen

The study will include 10,000 hypertensive or non-hypertensive individuals aged 55 years or over, at high risk of vascular disease. Following randomisation, treatment and follow-up of participants is scheduled to continue for an average of 5.5 years for the perindopril-indapamide versus placebo comparison, and at least 6 years for the intensive gliclazide MR-based therapy versus standard guidelines-based glucose lowering regimen comparison. The two primary outcomes are: first, a composite of stroke, myocardial infarction and cardiovascular death; and second, a composite of nephropathy and microvascular eye disease. An endpoint adjudication committee will review all primary study endpoints, blind to individuals' treatment allocations. A data and safety monitoring committee will periodically review unblinded data prior to completion of the

study. Final results from the study are first expected to be available in 2007 ~~2006~~. The trial will be conducted in approximately 200 clinical centres in about 20 countries in Australasia, Asia, Europe and North America.

Figure 2 Study periods

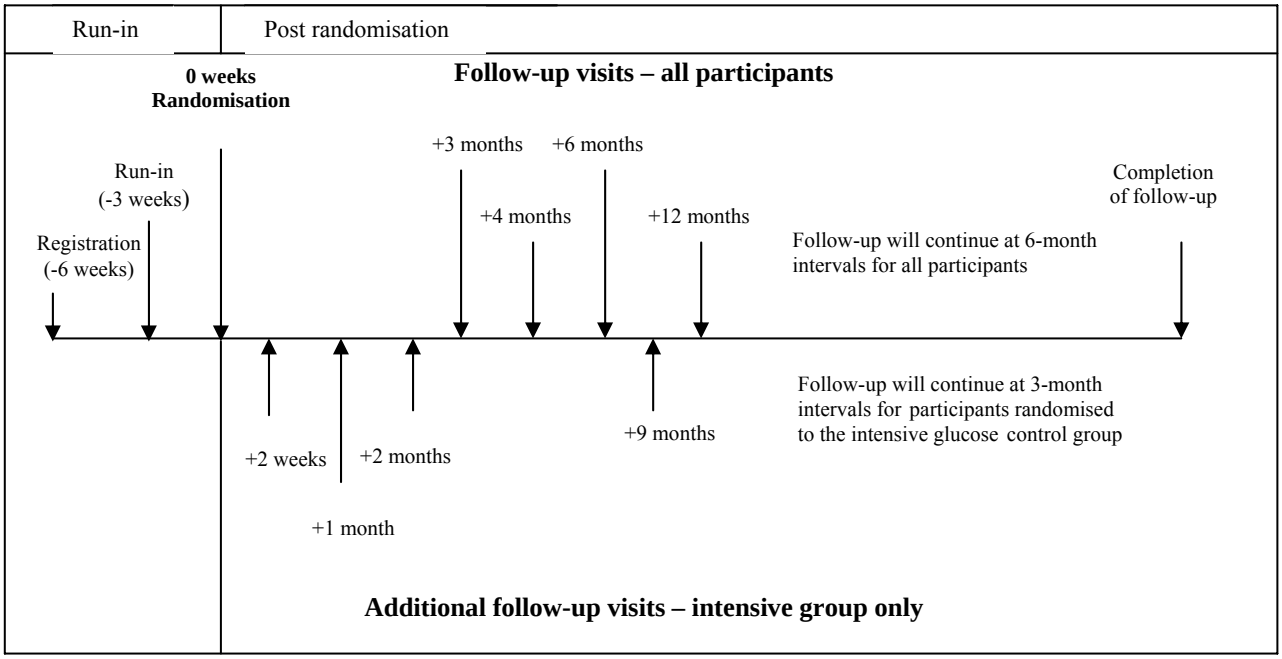
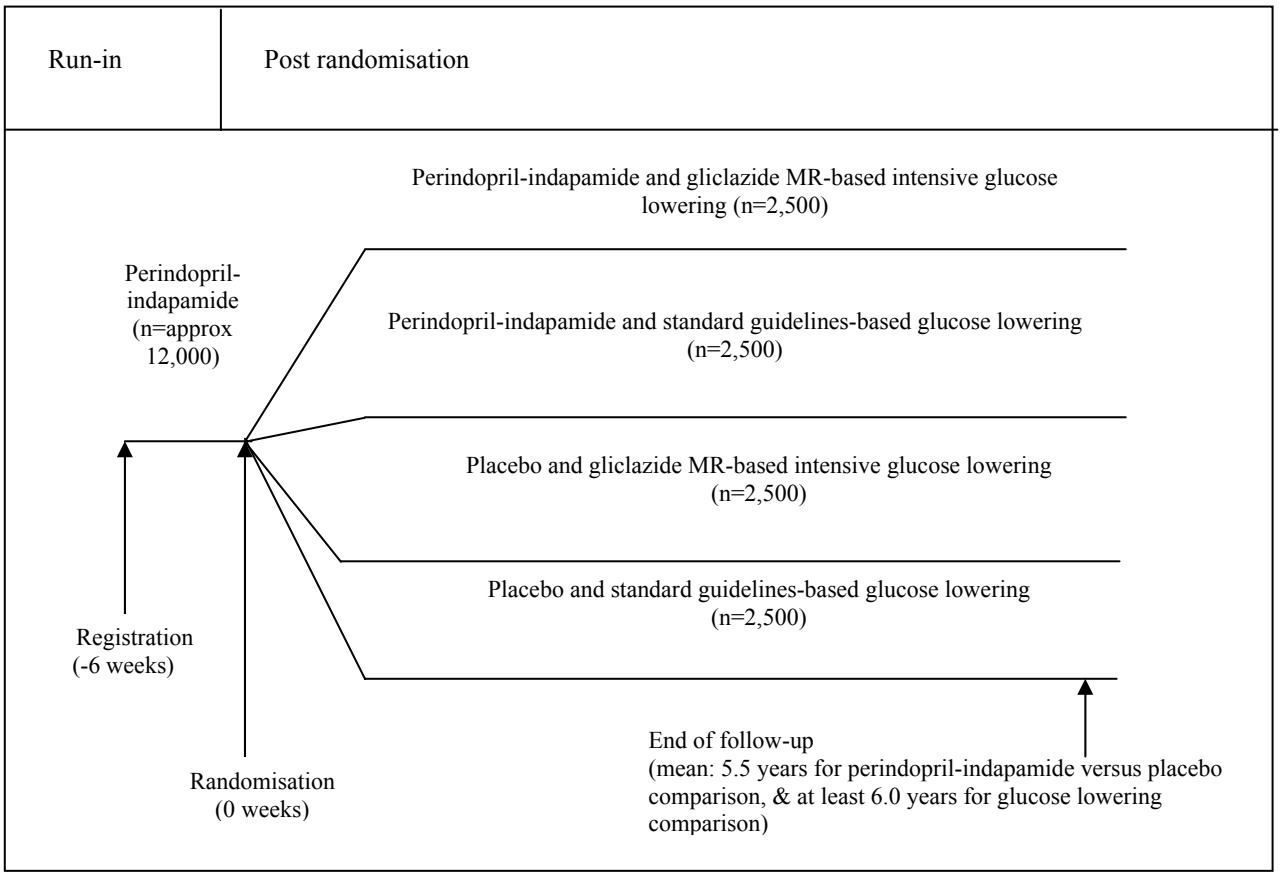


Figure 3 Study treatments



PARTICIPANTS

The trial will randomise and follow 10,000 individuals deemed eligible on the basis of the criteria listed below. Participants will only be enrolled if the responsible clinician has substantial uncertainty about the balance of benefits and risks likely to be conferred by the two study interventions when added to (or used to replace) whatever other therapy the participant is already receiving.

5.2.1 Inclusion criteria

- A diagnosis of type 2 diabetes mellitus first made at age 30 years or older
- Age 55 years or older at entry
- Ability to provide informed consent
- A substantially elevated risk of cardiovascular disease, indicated by:
  - *A history of major macrovascular disease* defined as any one of: stroke, myocardial infarction, hospital admission for transient ischaemic attack, hospital admission for unstable angina, coronary artery bypass graft, percutaneous transluminal coronary angioplasty (with or without stenting), peripheral revascularisation (angioplasty or surgery) or amputation secondary to vascular disease *or*
  - *A history of major microvascular disease* defined as any one of nephropathy (albumin:creatinine ratio >300μg/mg [33.9mg/mmol]),[61] retinal photocoagulation therapy, proliferative retinopathy (new blood vessels on the disc or elsewhere, vitreous haemorrhage, pre-retinal haemorrhage, or fibrous proliferations on the disc or elsewhere), macular oedema (retinal thickening within one disc diameter of the macular centre) or blindness in either eye (corrected visual acuity 6/60 or worse, persisting for three months or more) not known to be due to non-diabetic causes *or*
  - *A first diagnosis of type 2 diabetes made 10 or more years prior to entry or*
  - *Another major risk factor for vascular disease* defined as any one of: current daily cigarette smoking, total cholesterol greater than 6.0 mmol/l (with or without cholesterol lowering treatment), HDL cholesterol <1.0 mmol/l, microalbuminuria (albumin:creatinine ratio 30-300μg/mg [3.4-33.9mg/mmol])[61] *or*
  - *Age 65 years or over*

5.2.2 Exclusion criteria

- A definite contraindication to treatment with an ACE inhibitor or a thiazide-like diuretic
- A specific indication for treatment with an ACE inhibitor other than perindopril 2-4 mg daily (see also section 5.2.3) or a thiazide-like diuretic
- A definite and specific indication for, or contraindication to, treatment with gliclazide.
- A definite and specific indication for, or contraindication to, a haemoglobin A1c control target of 6.5% or less
- A definite indication for long-term therapy with full-dose or bed-time insulin
- Participation in another trial within the month prior to the Registration Visit or current participation in another trial

Other potential reasons for ineligibility include:

- High probability of non-adherence to study treatment or follow-up
- Current clinical instability (e.g. a major cerebral or coronary event or sight-threatening retinopathy or macular oedema within the previous few weeks)
- Life threatening non-vascular disease other than diabetes and its complications
- Moderate or severe dementia
- Major disability that is likely to prevent regular attendance at study clinics

Final decisions about eligibility are to be made at the discretion of the study investigator and the potential study participant, in the light of any requirements or guidance from local ethics committees and other regulatory bodies.

5.2.3 Special considerations in recruitment

The study inclusion and exclusion criteria have been designed to facilitate the recruitment of a broad cross section of high-risk individuals with type 2 diabetes. Notes about the recruitment of specific participant groups are provided below.

1. ***Hypertensive or non-hypertensive participants.*** Eligibility for the trial is not dependent on the level of blood pressure: any participant can be randomised if the responsible clinician has *uncertainty* about the balance of risks and benefits of adding the perindopril-indapamide combination to any other treatment already being provided.

2. ***Participants receiving an ACE inhibitor or other blood pressure lowering drugs.*** This study is designed to determine whether the addition of the perindopril-indapamide combination to background treatment with other therapies (including an ACE inhibitor wherever indicated) will improve important clinical outcomes. There is no restriction on the use of non-study blood pressure lowering drugs at entry except that potential participants must have no specific indication for either an ACE inhibitor other than perindopril at a dose of 2mg or 4mg daily or a thiazide-like diuretic.

   Eligible participants receiving treatment with an ACE inhibitor other than perindopril or a thiazide-like diuretic will therefore comprise either:

   - Those already prescribed an ACE inhibitor other than perindopril who can be switched to perindopril 2-4mg daily.

   - Those already prescribed a thiazide-like diuretic who can have the diuretic withdrawn and be switched to (or maintained on) a beta blocker, a calcium antagonist, an angiotensin II antagonist, perindopril 2-4 mg daily, or other agent as deemed appropriate by the responsible physician

3. ***Participants receiving oral therapy for glycaemic control.*** Eligibility for the trial is not dependent upon the type or number of oral agents used for glucose control or the entry level of either haemoglobin A_{1c} or fasting blood glucose. However, potential participants must have no specific indication for or contraindication to treatment with gliclazide or an intensive glucose-lowering regimen with target haemoglobin A_{1c} of 6.5% or less. Eligible participants receiving oral therapy for glycaemic control will therefore comprise either:

   - Those already prescribed a sulphonylurea (including gliclazide) who can be switched to gliclazide MR, (1-4 tablets daily) if randomised to the gliclazide MR-based intensive glucose lowering regimen.

   - Those already prescribed gliclazide who can be switched to another sulphonylurea or alternative glucose control regimen if randomised to standard guidelines-based therapy.

   - Those already prescribed another oral agent (such as metformin, acarbose or a thiazolidinedione) who can be switched to gliclazide MR or for whom gliclazide MR can be added if randomised to the gliclazide MR-based intensive glucose lowering regimen.

4. ***Participants receiving dietary therapy only.*** Such individuals are eligible for the study if the responsible clinician feels that treatment with gliclazide MR is not contraindicated.

5. ***Participants with evidence of macrovascular or microvascular disease.*** Individuals with evidence of macrovascular or microvascular complications of diabetes are eligible for inclusion in the study, except those meeting the exclusion criteria (see section 5.2.2).

5.3 STUDY TREATMENTS

5.3.1 Pre-randomisation

All potentially eligible participants will commence a 6-week run-in period during which they will receive open treatment with one tablet per day of the fixed low-dose perindopril-indapamide (2.0/0.625mg) combination. The 6-week run-in period will help to identify, before randomisation, those individuals who are unlikely to tolerate treatment with the fixed low-dose perindopril-indapamide combination or who are unlikely to comply with study treatment and follow-up procedures. To be eligible for randomisation, individuals must have tolerated the perindopril-indapamide combination and have taken more than 90% of all study tablets. During this period, participants will continue their usual glucose control therapy.

During the run-in period, participants treated with a thiazide-like diuretic must have that treatment either withdrawn or replaced by therapy with a beta-blocker, a calcium antagonist, an angiotensin II antagonist, perindopril 2-4mg daily, or other agent as deemed appropriate by the responsible physician.

During the run-in period, it will be necessary for all participants who require ACE inhibitor therapy to be stabilized on background treatment with perindopril 2-4mg daily (in addition to the fixed low-dose perindopril-indapamide combination).

The study sponsors will provide collaborating centres with perindopril 2-4mg daily for those patients for whom it is required.

5.3.2 Randomisation

Eligible individuals will be randomised to study treatments using a central, computer-based randomisation service accessible by internet and fax. The randomisation sequence will be formulated by the International Coordinating Centre and the randomisation service will be provided by the International Data Management Centre. Individuals will be randomised to the perindopril-indapamide combination or matching placebo and to the gliclazide MR-based intensive glucose control regimen or standard guidelines-based therapy in a 2 x 2 factorial design (Figure 4). Randomisation will be stratified by study centre, history of macrovascular disease or microvascular disease and background use of perindopril.

Figure 4 Factorial randomised treatment assignment

	Perindopril- indapamide	**Placebo**	**Number (intensive vs standard)**
Gliclazide MR-based intensive glucose control	Perindopril-indapamide plus Intensive glucose control	Placebo plus Intensive glucose control	5,000
Standard, guidelines-based glucose control	Perindopril-indapamide plus Standard glucose control	Placebo plus Standard glucose control	5,000
Number (perindopril-indapamide vs placebo)	5,000	5,000	10,000

5.3.3 Post-randomisation

Blood pressure lowering

Patients will be instructed to take the perindopril-indapamide/matching placebo tablets in the morning. All participants are randomly assigned to receive:

- ***Perindopril-indapamide combination.*** Each tablet contains 2mg perindopril and 0.625mg indapamide *(Preterax®*or *Predonium®)*. The study regimen will be one tablet daily for the first three months (2mg perindopril and 0.625mg indapamide) rising to two tablets daily thereafter (4mg perindopril and 1.25mg indapamide) unless a specific contra-indication to two tablets daily has arisen during the first three months of follow-up. The dose may be reduced to one tablet daily, at any time, if suspected intolerance of the higher dose develops.

or

- ***Matching placebo for perindopril-indapamide combination***. The study regimen will be one tablet daily for three months rising to two tablets daily thereafter. The dose may be reduced to one tablet daily in situations in which intolerance is suspected.

Background ACE inhibitor therapy
Participants for whom background ACE inhibitor therapy is definitely indicated will receive perindopril 2-4mg daily in addition to randomised treatment with the fixed low-dose perindopril-indapamide combination or placebo. Such treatment will be initiated and stabilized during the run-in period but may also be initiated at any time throughout follow-up at the discretion of the responsible physician. Perindopril will be available throughout follow-up for all participants continuing on randomised perindopril-indapamide/placebo but not for participants that have discontinued treatment with the perindopril–indapamide combination/placebo or for those that require a dose of perindopril greater than 4mg daily. If a higher dose of perindopril or another ACE inhibitor becomes definitely indicated during follow-up, then the perindopril-indapamide combination or its matching placebo must be discontinued.

Glucose Control
All participants are also randomly assigned to receive:-

- ***Gliclazide MR-based intensive glucose control targeting a haemoglobin A1c of 6.5% or less.*** Gliclazide MR will be provided in a modified-release formulation: each tablet contains 30mg of gliclazide and the dose range is 30-120mg (one to four tablets) daily in the morning. Any other suphonylurea (including any preparation of gliclazide) shall be discontinued at the randomisation visit and replaced with study gliclazide MR. The first dose may be 30-120mg daily depending upon previous treatment. Treatment with gliclazide MR should be continued throughout follow-up, with other agents (except other sulphonylureas) added as required to achieve the goal of a haemoglobin A1c of 6.5% or less (see Figure 5). In an effort to achieve this level of control, participants assigned this treatment will be subject to more intensive follow-up.

or

- ***Standard guidelines-based glucose control therapy.*** Participants assigned this regimen will continue to follow their usual glucose control program. The exception to this is participants currently prescribed gliclazide who must be changed to a glucose control regimen that does not include gliclazide (but that may include a different sulphonylurea). Wherever possible, the management of blood glucose levels among these participants should remain the responsibility of the doctors who provided the participants' diabetes care before inclusion in the study. At the discretion of these health care providers, glucose control should continue according to local, national or regional guidelines or other standard practice. To maximize the difference in mean haemoglobin A1c between the two groups, the study investigator will ideally not have direct responsibility for the management of glucose control among participants assigned to this regimen. Instead, the management of glucose levels in this group should be the responsibility of the physician usually responsible for the participant's diabetes care. If the same physician is responsible for glucose control in both groups it will be important that the glucose control targets and strategies for glucose management in each randomised group are clearly defined and different, such that the aims of the study are met. All other aspects of the participants care (e.g. use of other treatments such as lipid lowering, anti-platelet therapy, etc) should continue unchanged.

Strategies for achieving a haemoglobin A1c of 6.5% or less among participants assigned gliclazide MR-based intensive glucose control

Achieving and maintaining a haemoglobin A1c of 6.5% or less (the **target** level) will require careful dietary management as well as drug treatment. All participants assigned this regimen will receive gliclazide MR, which should be titrated up in dose (30-120 mg) in an effort to reduce haemoglobin A1c to the target level. Other agents such as metformin, thiazolidinediones and alpha-glucosidase inhibitors should be added at the discretion of the responsible physician if haemoglobin A1c remains above ~~7.5%~~ 7.0% (the **threshold** level). Alternatively, such agents can be introduced at lower levels of haemoglobin A1c (e.g. between 6.5 and ~~7.5%~~ 7.0%) if the responsible physician feels this appropriate. Whenever an additional agent is introduced, the dose should be titrated up in an effort to achieve the target glucose level. In the first few months, blood glucose levels are likely to provide a more useful basis for decisions about treatment titration than are levels of haemoglobin A1c. The target fasting blood glucose level for participants randomised to gliclazide MR-based intensive glucose control is ≤ 6 mmol/L (108 mg/dL).

Figure 5 Suggested titration protocol for the reduction of haemoglobin A1c levels to 6.5% or less

Haemoglobin Level	**Suggested Action**
Haemoglobin A1c **6.5% or less** (target level)	Maintain current therapy
Haemoglobin A1c **6.5% to 7.0%**	Titrate up or maintain existing therapy (if not at full dose)*
Haemoglobin A1c **7.0% or greater** (threshold level)	Titrate up existing therapy (if not at full dose) and/or introduce additional therapy (unless contraindicated)

Suggested drug treatment steps:

1. Add **gliclazide MR**
2. Increase the dose of **gliclazide MR** (30-120 mg)
3. Add or increase the dose of **metformin**†
4. Add or increase the dose of **thiazolidinedione**†
5. Add or increase the dose of **alpha-glucosidase inhibitor**†
6. Add **bed time insulin** therapy
7. Add a **full insulin** regimen or increasing the dose of a full insulin regimen

* Additional agents can also be introduced at the discretion of the responsible investigator
† Order of introduction at discretion of responsible physician

Dietary control should be reviewed and reinforced in all participants irrespective of the level of haemoglobin A1c

Other strategies that may help to achieve tight glucose control include:

- ***More frequent contact with diabetes care staff***. Among participants assigned the more intensive treatment regimen, clinic visits are scheduled such that follow-up is at least 3 monthly throughout the study, with additional visits at 2 weeks, 1 month and 2 months after randomisation. By contrast, in the standard guidelines-based glucose control group, the initial visits after randomisation will be at 3, 4 and 6 months and 6 monthly thereafter.
- ***Attendance at special glucose control clinics***. It is anticipated that all participants in the intensive treatment group will receive glucose control therapy through special glucose control clinics.
- ***Participant education materials***. Special participant education materials may be made available for specific use by the participants assigned the intensive blood glucose control regimen. Such materials may be developed specifically for the study or obtained from organisations experienced in the control of diabetes.

- ***Referral to diabetes self-help groups.*** Wherever possible, participants assigned the intensive glucose control regimen will be referred to diabetes self-help groups.
- ***Regular review by dietician and diabetes nurse***. Ancillary staff such as dieticians and specialist nurses may be able to provide additional advice about diet and weight control for participants assigned the intensive glucose control regimen.
- ***More frequent home monitoring of blood glucose levels***. Regular home blood glucose monitoring with self-referral thresholds and telephone follow-up by diabetes support staff may improve control and enhance adherence to participants assigned the intensive control regimen.

5.3.4 Premature discontinuation of randomised treatment

Either arm of the study (blood pressure lowering or glucose control) may be permanently or temporarily discontinued for a particular participant if a definite indication for, or contraindication to, any of the treatments becomes apparent. In general, if a treatment in one arm of the study becomes definitely indicated or definitely contraindicated then that arm should be discontinued but the other arm of the study should continue. For example, if a participant develops a typical ACE inhibitor cough of a severity requiring discontinuation of the perindopril-indapamide/placebo arm, then the glucose control arm should continue unchanged. The decision to discontinue either of the randomised treatments is at the discretion of the study participant and the responsible physician. However, wherever possible, randomised study treatments should be continued throughout follow-up and if discontinuation is necessary, the possibility of recommencing therapy should always be considered. If a participant becomes pregnant, all study treatments must be discontinued. **Regardless of whether the participant continues to adhere to one or both of the treatment arms, the follow-up schedule should continue unchanged for all randomised participants.** If any participant is not able to attend all the scheduled visits then as far as possible, follow-up should be completed by other means (e.g. alternate visits, home visits, telephone follow-up, through general practitioner or national morbidity/mortality registers).

5.3.5 Unblinding of perindopril-indapamide/placebo treatment allocation

An emergency unblinding facility will be maintained throughout the entire duration of the study by the Data Management Centre. The facility will be available 24 hours a day, 7 days a week, with access by telephone (or fax for non-English speaking investigators). In general, unblinding of participants should only be performed when knowledge of the treatment allocation will influence participant management: for example after overdose of the study treatment or placebo. Unblinding need not be performed if the perindopril-indapamide combination has become definitely indicated or definitely contraindicated, for example:

- If treatment becomes definitely indicated, then stop the perindopril-indapamide/placebo and commence active treatment, but do not unblind
- If treatment becomes definitely contraindicated, then discontinue the perindopril-indapamide/placebo but do not unblind

Aside from emergency unblinding, access to information about the treatment code will be restricted to those individuals providing the unblinding service and those individuals responsible for preparation of the interim analyses for the Data and Safety Monitoring Committee. The unblinding facility will be managed by the Data Management Centre and unblinding will be performed by individuals not otherwise involved in the day-to-day conduct of the study.

5.3.6 Study treatment manufacturing, packaging, labelling, distribution, dispensing and disposal

The study treatments are described above in section 5.3. Study treatments will be manufactured, packaged and labelled by Servier according to the requirements of the regulatory authorities in each of the participating countries and in compliance with the recommendations outlined in appendix 13 of the European Guide to Good Manufacturing Practice. The International Coordinating Centre will liaise with Servier, the Regional Coordinating Centres and the Local Clinical Centres to facilitate this process.

For the open run-in period, fixed low-dose perindopril-indapamide (2mg/0.625mg) combination will be provided in a box containing 2 blisters of 30 tablets. For those participants that require open treatment with active perindopril (2mg or 4mg daily), perindopril will be provided in a box containing 4 blisters of 30 tablets.

For the post-randomisation period, double-blind fixed low-dose perindopril-indapamide (2mg/0.625mg) combination or matching placebo will be provided in 6-month packs comprising a large box containing two smaller boxes with 3 months supply in each. Each 3 months supply will consist of 7 blisters of 30 tablets each. Open gliclazide MR will be provided in 6-month packs comprising a large box containing two smaller boxes with 3 months supply in each. Each 3 months supply will consist of 14 blisters of 30 tablets each. For those participants that require open treatment with active perindopril (2mg or 4mg daily), 6 month packs of perindopril will be provided in two boxes each containing 4 blisters of 30 tablets.

At the first end-of-study visit, for those participants that require open treatment with active perindopril-indapamide (2mg/0.625mg: one or two tablets daily), 6 month packs will be provided in one large box containing two smaller boxes with 3 month supply in each. Each 3 month supply will consist of 7 blisters of 30 tablets each.

Distribution of all study treatments will be the responsibility of Servier or a designated subcontractor under the direction of the International Coordinating Centre. The International Coordinating Centre will monitor the requirements of the Local Clinical Centres for study treatments and provide Servier with instructions for manufacture and distribution of study treatments.

Arrangements for dispensing of study treatments at the Local Clinical Centres will be at the discretion of the responsible investigator in compliance with the relevant regulatory requirements and the protocol. In general, secure storage and dispensing of drugs and the associated documentation will be the responsibility of the pharmacy department at the Local Clinical Centre. Study treatments will only be dispensed to study participants.

Unused perindopril-indapamide/placebo, gliclazide MR and perindopril will be collected from study participants by the Local Clinical Centre staff and uplifted by Servier who will be responsible for counting the tablets returned and overseeing their destruction. Servier will be responsible for documentation of study drug disposal, which will be performed in accordance with the regulatory requirements of the Local Clinical Centre.

5.3.7 Measurement of adherence

Adherence will be determined during the run-in period and only those participants who take 90% or more of the study tablets will be eligible for randomisation. After randomisation, adherence to study treatments will be assessed at scheduled visits throughout follow-up by questioning the participant and recording the number of tablets taken. If treatment is discontinued prior to the completion of scheduled follow-up, the date on which tablets were last taken and the main reason for premature discontinuation of the study treatment will be recorded. For the open comparison of glucose control strategies, adherence will be assessed through monitoring of blood glucose and haemoglobin A_{1c} levels as well as through recording of the number of gliclazide MR tablets taken.

5.4 STUDY OUTCOMES

5.4.1 Primary outcomes

There are two primary study outcomes for each randomised comparison:

1. The composite of non-fatal stroke, non-fatal myocardial infarction and death from any cardiovascular cause, where:
   - Non-fatal stroke is a non-fatal event with a Ninth International Classification of Diseases (ICD 9) code of 430-435 or 437-438 (i.e. not including transient ischaemic attack). Subarachnoid haemorrhage is not included in the primary outcome definition of stroke.
   - Non-fatal myocardial infarction is a non-fatal event with an ICD 9 code of 410.
   - Death from any cardiovascular cause is a fatal event with an ICD 9 code of 394-459 (diseases of the circulatory system) or 798.9 (sudden death).
2. The composite of new or substantially worsening nephropathy or microvascular eye disease, where:
   - New or worsening nephropathy is defined as any of the following:
     - the development of macroalbuminuria (albumin:creatinine ratio >300μg/mg [33.9mg/mmol]), confirmed by two positive results[61]
     - a doubling of serum creatinine to a level of at least 200μmol/l
     - the requirement for renal replacement therapy (dialysis or transplantation)
     - death from renal disease
   - New or worsening eye disease is defined as any of the following:
     - the requirement for retinal photocoagulation therapy,
     - the development of proliferative retinopathy (new blood vessels on the disc or elsewhere, vitreous haemorrhage, pre-retinal haemorrhage, or fibrous proliferations on the disc or elsewhere), in a participant known not to have this condition at entry
     - the development of macular oedema (retinal thickening within one disc diameter of the macular centre), in a participant known not to have this condition at entry
     - the development of diabetes-related blindness in either eye (corrected visual acuity 6/60 or worse, persisting for three months or more and known not to be due to non-diabetic causes as defined above), in a participant known not to have this condition at entry

Evidence about suspected primary outcome events will be reviewed by the Endpoint Adjudication Committee whose members are blinded to participants' treatment allocation. This committee will make final decisions as to whether the evidence about any one event is sufficient to meet the criteria for a primary outcome event.

5.4.2 Secondary outcomes

The secondary outcomes for each randomised comparison include:

- *Major cerebrovascular disease* events including death from cerebrovascular disease and non-fatal stroke
- *All cerebrovascular disease* events including death from cerebrovascular disease, non-fatal stroke, transient ischaemic attack [defined as acute disturbance of focal neurological or monocular (amaurosis fugax) function with symptoms lasting less than 24 hours and thought to be due to vascular disease of an arterial, embolic or thrombotic kind] and sub-arachnoid haemorrhage
- *Major coronary heart disease* events including death from coronary heart disease, sudden death (otherwise unexplained) and non-fatal myocardial infarction.
- *All coronary heart disease* events including death from coronary heart disease, sudden death, non-fatal myocardial infarction, silent myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty (with or without stenting) and hospitalisation for unstable angina
- *All heart failure* events leading to death, requiring hospital admission or resulting in an increase in NYHA class

- *All peripheral vascular disease* events including death due to peripheral vascular disease, amputation of at least one digit, requirement for a peripheral revascularisation procedure (surgery, angioplasty or emergency thrombolysis), or chronic ulceration of a lower limb thought due to arterial insufficiency
- *All cardiovascular disease* events including all cerebrovascular disease, all coronary heart disease, all heart failure, and all peripheral vascular disease (as defined above)
- *Death from any cardiovascular cause*
- *Death from any cause*
- *Hospital admission* of 24hrs or longer for any cause
- *Microalbuminuria* defined as an albumin:creatinine ratio of 30-300µg/mg [3.4-33.9mg/mmol], confirmed by two positive results in a participant without either macroalbuminuria or microalbuminuria at entry
- *Visual deterioration* defined as a decrease of two lines in best vision (corrected or through a pin-hole) in either eye
- New or worsening *neuropathy* defined as the development of new or worsening loss of tactile sensation, new or worsening loss of ankle or knee reflexes, or impotence in a participant without the condition at entry
- *Cognitive function* measured by Folstein Mini-Mental State Examination
- *Dementia* diagnosed by a suitably qualified specialist and satisfying the criteria provided by the fourth edition of the Diagnostic Statistical Manual of Mental Disorders (DSM- IV)

5.4.3 Other parameters for assessment

- Hypoglycaemia defined on the basis of a laboratory measured low blood glucose level <50 mg/dL and/or an episode with typical signs and symptoms which may be self reported, and classified as either:
  - *Major hypoglycaemia* – a hypoglycaemic episode associated with transient CNS dysfunction without other apparent cause, in which the individual was unable to treat him/herself and had help from another person (e.g. to administer glucose or glucagon)

  or
  - *Minor hypoglycaemia* – a hypoglycaemic episode associated with transient CNS dysfunction or other typical signs or symptoms without other apparent cause, in which the individual was able to treat him/herself (e.g. with food or glucose)
- Adherence to study treatment defined as the proportion of scheduled tablets taken
- Tolerability of study treatment defined as the proportion of participants continuing on study treatment

5.4.4 Quality of life and health care utilisation

Data on quality of life will be recorded using standard instruments such as the EuroQol and SF-36 questionnaire. All hospital medical care will be recorded routinely on the case record forms at study visits. Non-hospital medical care will be assessed in Australia only using the national Medicare data base (Australian participants will be asked to provide consent for this additional data collection).

5.4.5 Reporting of study outcomes and serious adverse events

Information about the occurrence of study outcomes and all other serious adverse events will be sought at all scheduled visits. Serious adverse events should be reported at the time of occurrence between visits. Study outcomes are defined above (section 5.4) and serious adverse events are defined as all those other events that:

- result in death
- are life threatening in the opinion of the responsible investigator (i.e. the participant was at risk of death at the time of the event. It does not refer to an event that might hypothetically have caused death had it been more severe)
- require inpatient hospitalisation or prolongation of existing hospitalisation
- result in persistent or significant disability or incapacity
- result in congenital anomaly or birth defect (unlikely since participants must be aged 55 years or over at entry)

- are important medical events in the opinion of the responsible investigator (i.e. any event that is not immediately life-threatening and does not result in death or hospitalisation but which may jeopardise the participant or may require intervention to prevent one of the other outcomes listed above)

When a study outcome or serious adverse event occurs, the responsible investigator should ensure that the serious adverse event is reported immediately to the International Data Management Centre by completing a Serious Adverse Event Form. The International Coordinating Centre will ensure that information about serious suspected adverse drug reactions is forwarded to Servier whose responsibility it is to inform regulatory bodies, as required.

The Investigator will ensure that there is adequate follow-up of each participant who has a study outcome or other serious adverse event. In addition, the Investigator must ensure that all regulatory requirements specified by other relevant local bodies are completed. Documentation about each serious adverse event that is a suspected primary study outcome must be provided to the International Coordinating Centre, which will in turn provide copies to the Endpoint Adjudication Committee. Source documentation about all such events will be retained in the participant's case record folder, which will be stored for at least 15 years.

Serious adverse events that occur within 15 days after the end of scheduled follow-up will be reported in the same way as those that occur before the end of follow-up. In addition, any adverse event that occurs after the completion of scheduled follow-up, and that the Investigator believes is due to the study treatments will also be reported in the same way.

The Data and Safety Monitoring Committee will regularly review all such events.

5.5 STUDY VISITS

All study participants will be seen on two occasions prior to the randomisation visit. After randomisation, the schedule of visits will be different in the two glucose control groups:

- those assigned the gliclazide MR-based intensive glucose lowering regimen will be seen at least once every three months
- those assigned standard guidelines-based therapy will be seen 6-monthly (except during the first 6 months when there will be visits 3 and 4 months after randomisation)

For all randomised participants, the scheduled average post-randomisation follow-up period will be:

- 5.5 years for the perindopril-indapamide versus placebo comparison, with an estimated maximum follow-up of 6 years and an estimated minimum follow-up of 4.25 years among those surviving to the end of scheduled follow-up
- at least 6 years for the gliclazide MR-based intensive glucose control versus standard guidelines-based therapy, with an estimated maximum follow-up of 6.5 years and an estimated minimum follow-up of 4.75 years among those surviving to the end of scheduled follow-up.

In general visits should be arranged for within ± 2 weeks of the scheduled visit date.

5.5.1 Baseline

[Visit 1(-6 weeks): for all potential participants]
Potentially eligible individuals will attend the study clinic 6 weeks before randomisation. At this initial visit, the study staff will provide the potential participant with whatever information is required for him or her to make an informed decision about participation with due regard for local regulatory requirements. At this visit the study staff will:

Consent and medical history

- Obtain signed informed consent prior to participation in the study [to include consent to conduct analyses of genetic polymorphisms (Appendix 1)]
- Determine history of diabetes including duration, current treatment, complications, signs and symptoms (of diabetes and complications), family history of diabetes

- Record general medical history including history of hypertension, cerebrovascular diseases, coronary heart disease and current medications
- Collect lifestyle information about factors such as smoking, alcohol consumption and exercise
- Make an assessment of cognitive function using the Folstein Mini–Mental State Examination. If the score is less than 24 or if the investigator believes that the participant might have dementia, the potential participant will be referred to a suitably qualified specialist for assessment and diagnosis based on the DSM IV criteria for dementia
- Assess dependency based on the requirement for help with activities of daily living in the preceding two weeks
- Collect information about quality of life from self administered questionnaires
- Record glucose lowering treatments
- Record other concomitant treatments

Blood pressure, ophthalmoscopy and general examination

- Measure height, weight, heart rate and blood pressure. Systolic and diastolic blood pressure will be measured three times using an Omron automated sphygmomanometer, after 5 minutes rest with the participant in the seated position (Appendix 6).
- Measure visual acuity and conduct fundoscopy for assessment of eye disease (or record the findings of an earlier assessment conducted within the last 6 months)
- Perform a general physical examination including assessment of loss of tactile sensation, loss of ankle or knee reflexes, loss of peripheral pulses and lower limb ulceration
- Record a resting 12 lead ECG (or record the findings of an earlier ECG conducted within the last 3 months)

Blood samples and urinalysis

- Collect a blood sample for local measurement of haemoglobin A1c, creatinine, sodium, potassium and ALT
- Collect a fasting blood sample for local measurement of glucose, triglycerides, total cholesterol, LDL cholesterol (calculated), HDL cholesterol (if a fasting sample is not obtained at this visit, it must be obtained at Visit 2, -3 weeks).
- Identify macroalbuminuria or microalbuminuria based on urinary albumin:creatinine ratio from a random urine sample, confirmed by two positive results (laboratory measurement, infection excluded, collected within the last 3 months) (if not obtained at this visit or within last 3 months, sample must be obtained at Visit 2, -3 weeks)
- Collect a fasting blood sample (about 20mls) for separation, aliquoting and frozen storage prior to shipment to the central laboratory. Preparation of these samples will be performed at the Local Clinical Centre with aliquots deep-frozen (at least -20°C and preferably -70°C) and stored at the Local Clinical Centre. Samples will be transferred deep-frozen from the centres once or twice during recruitment. The purpose of this sample collection is to allow central analyses of potential biochemical, haematological and genetic factors that may predict the occurrence of macrovascular and microvascular complications of diabetes and other serious illnesses (if a fasting sample is not obtained at this visit, it must be obtained at Visit 2, -3 weeks).

Dispensing study tablets and managing concurrent therapy

- Provide run-in supply of tablets of the fixed low-dose perindopril-indapamide (2.0mg/0.625mg) combination and instruct the potential participant to take one tablet daily until the next assessment at -3 weeks.
- Determine requirement for background ACE inhibitor therapy. If ACE inhibitor therapy is indicated then initiate or replace current treatment with 2mg or 4mg perindopril daily. Provide sufficient perindopril for the entire run-in period.
- Withdraw treatment with a thiazide-like diuretic and replace by therapy with a beta-blocker, a calcium antagonist, an angiotensin II antagonist, perindopril 2-4mg daily, or other agent as deemed appropriate by the responsible physician.

Complete the Visit 1, Baseline Assessment Form.
Register the potential participant

5.5.2 Run-in

[Visit 2 (-3 weeks): for all potential participants]
At this visit, 3 weeks after the start of run-in therapy, the study staff will:

- Inquire about possible intolerance of the study run-in treatment
- Inquire about the occurrence of serious adverse events

- Review the results of the Visit 1 blood tests
- Collect a blood sample for local measurement of creatinine, sodium and potassium
- If **not** taken at Visit 1 (-6 weeks), collect a fasting blood sample for local measurement of haemoglobin A1c, glucose, triglycerides, total cholesterol, LDL cholesterol (calculated), HDL cholesterol
- If **not** taken at Visit 1 (-6 weeks) and results not available from assessment within the past 3 months, identify macroalbuminuria or microalbuminuria based on urinary albumin:creatinine ratio from a random urine sample, confirmed by two positive results (laboratory measurement, infection excluded)
- If **not** taken at Visit 1 (-6 weeks), collect a fasting blood sample (about 20mls) for separation, aliquoting and frozen storage prior to shipment to the central laboratory.

- Measure systolic and diastolic blood pressure and heart rate

- Confirm continued eligibility for the study
- Instruct the potential participant to continue taking one tablet daily of the low-dose perindopril-indapamide (2.0mg/0.625mg) combination and to continue treatment with background perindopril, where applicable, until the next assessment at 0 weeks.

Complete the Visit 2, Run-In Form

5.5.3 Randomisation

[Visit 3 (0 weeks): for all potential participants]
At this visit, 6 weeks after the start of run-in therapy, the study staff will:

For all participants:

- Confirm that adherence to study treatment has been good (90% or more tablets taken).
- Inquire about possible intolerance of the study run-in treatment
- Inquire about the occurrence of serious adverse events

- Review the results of the Visit 2 blood tests
- Measure venous or capillary blood glucose
- Measure systolic and diastolic blood pressure and heart rate
- Record glucose lowering treatments

- Confirm the participant's eligibility for the study and their willingness to participate
- Randomise eligible participants
- Dispense 6 months supply of double-blind perindopril-indapamide/placebo and instruct the participant to take one tablet daily, in the morning
- Dispense open label perindopril 2-4mg, where applicable

For participants assigned the intensive glucose control regimen:

- Advise the participant that their diabetic care will now be intensified
- Review level of haemoglobin A1c from baseline blood tests
- Inquire about recent glucose control

- Develop strategy for control of haemoglobin A1c to 6.5%. Add glucose control therapy as required and encourage the participant to make use of home glucose monitoring (see section 5.3.3).
- Consider referral to dietician and other diabetes care support staff
- Discontinue therapy with sulphonylureas other than gliclazide MR
- Dispense 6 months supply of gliclazide MR at a dose of 30-120 mg and instruct the participant to take one to four tablets daily, in the morning

For participants assigned the standard glucose control regimen:
- Switch participants on any preparation of gliclazide to a different sulphonylurea
- Advise the participant that their diabetic care will remain unchanged at present and advise the participant to continue with usual glucose control practices. Arrange follow-up diabetic care as usual for the participant

Complete the Visit 3, Randomisation Form

5.5.4 2 weeks

[Visit 4 (+2 weeks): for participants randomised to intensive glucose control group only]
After 2 weeks of randomised treatments, the study staff will see participants assigned the intensive glucose control regimen. The principal purpose of this visit is to check that there is good control of blood glucose and to make any changes necessary to improve control. At this visit the study staff will:
- Confirm that adherence to study treatments has been good

- Measure and review level of venous or capillary blood glucose
- Measure systolic and diastolic blood pressure and heart rate

- Record glucose control strategy since last visit
- Inquire about recent glucose control
- Consider referral to dietician and other diabetes care support staff

- Modify intensity of glucose control regimen as required to achieve a haemoglobin A1c level of 6.5% or less

Complete the Visit 4, 2 Week Follow-up Form.

5.5.5 1 and 2 months

[Visits 5 and 6 (+1 month and +2 months): for participants randomised to intensive glucose control group only]
One and two months after randomisation, the study staff will see participants assigned the intensive gliclazide MR-based regimen. At these visits, the study staff will:
- Confirm that adherence to study treatment has been good

- Measure and review level of venous or capillary blood glucose
- Measure and review level of haemoglobin A1c
- Measure systolic and diastolic blood pressure and heart rate

- Record glucose control strategy since last visit
- Inquire about recent glucose control
- Consider referral to dietician and other diabetes care support staff

- Modify intensity of glucose control regimen as required to achieve a haemoglobin A1c level of 6.5% or less

Complete the Visit 5 or 6, 1-month or 2-month Follow-up Form.

5.5.6 3 months

[Visit 7 (+3 months): for all participants]

At 3 months the study staff will:

For all participants:
- Confirm that adherence to the perindopril-indapamide/placebo study treatment has been good
- Inquire about possible intolerance of the perindopril-indapamide/placebo study treatment
- Inquire about the occurrence of study outcomes and serious adverse events
- Inquire about the occurrence of hypoglycaemic episodes
- Measure systolic and diastolic blood pressure and heart rate

- Advise the participant to increase the dose of perindopril-indapamide/placebo to two tablets daily unless there is a specific contraindication to the increased the dose

For participants assigned the intensive glucose control regimen:
- Confirm that adherence to the intensive glucose control regimen has been good

- Measure and review level of venous or capillary blood glucose
- Measure and review level of haemoglobin A1c

- Record glucose control strategy since last visit
- Inquire about recent glucose control
- Consider referral to dietician and other diabetes care support staff

- Modify intensity of glucose control regimen as required to achieve a haemoglobin A1c level of 6.5% or less

Complete the Visit 7, 3-month Follow-up Form

5.5.7 4 months

[Visit 8 (+4 months): for all randomised participants]
At 4 months the study staff will:

For all participants:
- Confirm that adherence to the perindopril-indapamide/placebo study treatment has been good
- Inquire about possible intolerance of the perindopril-indapamide/placebo study treatment
- Inquire about the occurrence of study outcomes and serious adverse events
- Inquire about the occurrence of hypoglycaemic episodes

- Measure systolic and diastolic blood pressure and heart rate
- Collect a blood sample for local measurement of creatinine, sodium and potassium

- Advise the participant to continue to take two tablets of perindopril-indapamide/placebo daily, unless there is a specific contraindication to continuation at this dose

For participants assigned the intensive glucose control regimen:
- Confirm that adherence to the intensive glucose control regimen has been good

- Measure and review level of venous or capillary blood glucose
- Review level of haemoglobin A1c

- Record glucose control strategy since last visit
- Inquire about recent glucose control
- Consider referral to dietician and other diabetes care support staff

- Modify intensity of glucose control regimen as required to achieve a haemoglobin A1c level of 6.5% or less

Complete the Visit 8, 4-month Follow-up Form

5.5.8 6 months

[Visits 9 (+6 months) onwards: for all randomised participants]
At 6 months and at 6-monthly intervals thereafter (for a total of 3 to 6 years, with a mean of 5.5 years) the visits will follow the same format, except for variations at annual and biennial visits, which are described in sections 5.5.9 and 5.5.10 below. At the 6 monthly assessments the study staff will:

For all participants:
- Confirm that adherence to the perindopril-indapamide/placebo study treatment has been good
- Inquire about possible intolerance of the perindopril-indapamide/placebo study treatment
- Inquire about the occurrence of study outcomes and serious adverse events
- Inquire about the occurrence of hypoglycaemic episodes

- Measure systolic and diastolic blood pressure and heart rate
- Measure the weight of the participant
- Record glucose lowering treatments
- Record other concomitant treatments

- At visit 9 (+6 months) measure haemoglobin A1c

- Dispense 6 months supply of double-blind perindopril-indapamide/placebo and instruct the participant to take two tablets daily, in the morning, unless there is a specific contraindication to continuation at this dose
- Dispense open label perindopril 2-4mg, where applicable

For participants assigned the intensive glucose control regimen:
- Confirm that adherence to the intensive glucose control regimen has been good

- Measure and review level of venous or capillary blood glucose
- Measure and review level of haemoglobin A1c

- Record glucose control strategy since last visit
- Inquire about recent glucose control
- Consider referral to dietician and other diabetes care support staff

- Modify intensity of glucose control regimen as required to achieve a haemoglobin A1c level of 6.5% or less
- Dispense 6 months supply of gliclazide MR at a dose of 30-120 mg and instruct the participant to take one to four tablets daily, in the morning

Complete the relevant visit Follow-up Form

5.5.9 Annual visits

[Visits 11, 15 and 19 (+12, +24 and +36 months) for all randomised participants, and visits 23, 27 and 31 (+48, +60 and +72 months) for the subset of participants reaching these visits]
In addition to the assessments outlined in section 5.5.8, at annual visits the study staff will:
- Collect a blood sample for local measurement of creatinine, sodium and potassium
- Measure level of haemoglobin A1c
- At Visit 11, +12 months only, in a random sample of 10 percent of participants (to be selected by the International Coordinating Centre), an additional fasting blood sample of approximately 30mls will be collected to assess measurement variability: 20mls will be separated and shipped deep-frozen to the

central laboratories and 10mls will be analysed locally to determine the levels of glucose, total cholesterol, LDL cholesterol (calculated), HDL cholesterol and triglycerides.

Complete the relevant visit Follow-up Form

5.5.10 Biennial visits

[Visits 15 and 23 (+24, and +48 months) for all randomised participants. Surviving participants that do not reach visit 23 (+48 months) will have the additional assessments carried out at the final visit. Visit 31 (+72 months) for the subset of participants reaching this visit]

In addition to the assessments outlined in section 5.5.8, at biennial visits the study staff will:

- Collect lifestyle information about factors such as smoking, alcohol consumption and exercise
- Assess cognitive function using the Folstein Mini-mental state examination (if the MMSE score is less than 24 or if the responsible clinician feels that the participant may be demented, the participant will be referred to an appropriately qualified specialist for assessment and diagnosis of dementia using the DSM IV criteria – unless a previous firm diagnosis of dementia has been made)
- Assess dependency based on the requirement for help with activities of daily living in the preceding two weeks
- Collect information about quality of life obtained from self administered questionnaires

- Measure visual acuity and conduct fundoscopy for assessment of eye disease
- Perform a general physical examination including assessment of loss of tactile sensation or temperature sensitivity, loss of ankle or knee reflexes, loss of peripheral pulses and lower limb ulceration
- Record a resting 12 lead ECG
-
- Collect a fasting blood sample for local measurement of triglycerides, total cholesterol, LDL cholesterol (calculated), HDL cholesterol, ALT
- Assess macroalbuminuria or microalbuminuria from urinary albumin:creatinine ratio in a random urine sample, confirmed by two positive results (laboratory measurement, infection excluded)
- Measure and review level of venous or capillary blood glucose

Complete the relevant visit Follow-up Form

5.5.11 Other regular visits

[Visits 10, 12, 14, 16 and 18 (+9, +15, +21, +27 and +33 months) for participants randomised to the intensive glucose control group only and visits 20, 22, 24, 26, 28 and 30 (+39, +22, +51, +57, +63 and +69 months) for the subset of participants reaching these visits]

At these visits, the study staff will:

- Confirm that adherence to study treatment has been good

- Review level of venous or capillary blood glucose
- Measure and review haemoglobin A1c
- Measure and review fasting blood glucose

- Record glucose control strategy since last visit
- Inquire about recent glucose control
- Consider referral to dietician and other diabetes care support staff

- Modify intensity of glucose control regimen as required to achieve a haemoglobin A1c level of 6.5% or less

Complete the relevant visit Follow-up Form

5.5.12 Final visit

[For the final follow-up visit for each randomised treatment comparison]
At both end-of-study visits, except for the provision of study drugs, the study staff will collect the same data as for a 6 month visit (see section 5.58), and in addition will:

- Measure plasma creatinine
- Measure visual acuity
- Assess macroalbuminuria or microalbuminuria from urinary albumin:creatinine ratio in a random urine sample, confirmed by two positive results (laboratory measurement, infection excluded)

At the first end-of-study visit (perindopril-indapamide versus placebo), the study staff will also:

- Discontinue randomised perindopril-indapamide or matching placebo, and commence open-label perindopril-indapamide, if indicated in the opinion of the responsible investigator
- Continue to provide or commence open-label background perindopril, if indicated in the opinion of the responsible investigator.

At the final end-of-study visit (gliclazide MR-based intensive glucose control versus standard guidelines-based glucose control), the study staff will also discontinue all study drugs.

5.6 QUALITY ASSURANCE

The study will be conducted in accordance with the International ICH Guidelines for Good Clinical Research Practice and with all relevant local, national and international regulations.

5.6.1 Monitoring of study centres

Prior to initiation of the study at any Local Clinical Centre, the Investigator will be trained in the methods of the study and the Local Clinical Centre will be visited by a representative of the Regional Coordinating Centre and/or International Coordinating Centre to ensure that the site has adequate facilities and resources to carry out the study. In addition, all Investigators will be provided with materials detailing all study procedures. Before initiating the study, the Investigator and any co-investigators will sign and provide to the International Coordinating Centre, in English, an up-to-date curriculum vitae (CV). The CVs of other staff at the site that become involved in the study will be collected during the course of the study.

During the study, representatives of the Regional Coordinating Centre and/or International Coordinating Centre will visit all study centres on at least 3 occasions in the first year and on at least two occasions each year thereafter. The purpose of these visits will be to ensure that the study is conducted according to the protocol, good clinical practice guidelines and relevant regional regulatory requirements and to review study records and source documents for the specific verification of participant details, data quality and the completeness of follow-up. A report of each visit will be prepared by the monitor and reviewed by the International Coordinating Centre staff. In addition, the study may also be audited by inspectors appointed by Servier or by government regulatory authorities. Access to case record forms, source documents and other study files must be made available at all study sites for monitoring and audit purposes at reasonable times during the course of the study and after its completion.

The specific aims of the monitoring program will be to:

- confirm the existence of every participant
- confirm that informed consent has been obtained for every participant
- confirm the diagnosis of diabetes in every participant
- review source documents for every primary outcome
- review key data from a random sample of all participants

At completion of the study, the monitor will ensure that there are plans in place for the long-term storage of all the relevant data and source documentation (for 15 years).

5.6.2 Data management and coding

Data management will be provided by the Data Management Centre in association with the International Coordinating Centre. The principle means of data collection and data processing will be electronic via the Internet. Hard copies of the data may be printed and stored by each Local Clinical Centre to comply with local regulatory requirements. All computerised forms will be electronically signed by the authorised study staff and all changes made following the electronic signing will have an electronic audit trail with a signature and date. Centralised coding of outcomes will be performed by a trained medical coder but, wherever possible, codes will be assigned at the time of data entry.

5.6.3 Standardization of outcome assessment

An Endpoint Adjudication Committee will review information about every primary outcome reported in order to ensure that all endpoints meet standard diagnostic criteria. The committee will comprise experts in diabetes, cerebrovascular disease and coronary heart disease. The members of the Endpoint Adjudication Committee will be provided with explicit instructions about the adjudication of events and a manual detailing the criteria to be followed. These criteria will be determined jointly by the Management Committee and the Endpoint Adjudication Committee.

5.6.4 Standardization of haemoglobin A_1c assays

Haemoglobin A_1c assays will be performed at each of the Local Clinical Centres participating in the study. The method of assay employed in each centre will be identified and *wherever possible* the method used will be that recommended in the guidelines provided by the United States National Glycohaemoglobin Standardisation Program (based at the DCCT laboratory). The methods used by each laboratory will be recorded and copies of usual certificates of validation will be stored in the study file at each centre and in sponsor file. Reference samples from an accredited external quality assurance service will be assayed at each laboratory. If differences between techniques are known (or discovered through assay of reference samples) to result in predictably different results these will be controlled for in analyses, as required.

5.7 STATISTICAL ISSUES

5.7.1 Statistical power

The study has been designed to provide at least 90% power (with α=5%) to detect a 16% or greater reduction in the relative risk of each of the primary outcomes in each of the randomised comparisons.

5.7.2 Expected event rates

These power calculations assume a 3% (or more) annual event rate for each of the two primary outcomes among participants assigned the control condition (i.e. placebo or standard guidelines-based glucose control). This will provide a total of at least 640 events of each type (macrovascular and microvascular) among participants assigned the control conditions. Event rates among diabetic participants in HOPE suggest that these are plausible expectations.

5.7.3 Expected changes in blood pressure and haemoglobin A_1c

The power calculations also assume that there will be an average reduction in systolic blood pressure of at least 6 mmHg among participants assigned the perindopril-indapamide combination compared with those assigned placebo, and an average reduction in haemoglobin A_1c of at least 1% among participants assigned the intensive glucose control regimen compared with those assigned standard guidelines-based care. These estimates assume that full adherence to the perindopril-indapamide combination would result in reductions in systolic blood pressure of at least 8 mmHg and that three-quarters of all participants would remain adherent throughout follow-up. They also assume that full adherence to the intensive gliclazide MR-based regimen would result in a reduction in haemoglobin A_1c of at least 1.25% and that two thirds of all participants would remain adherent throughout follow-up.

5.7.4 Statistical analysis

The main effects and interactions of the study treatments for each of the primary outcomes, considered separately and jointly, will be determined using Cox models for survival data.. Analyses of secondary outcomes will be conducted using standard statistical procedures applicable to dichotomous, categorical or continuous data as appropriate. Primary analyses of efficacy and safety will include all randomised participants. The analyses will be conducted using SAS (Version 6 or later), S-plus and other standard statistical packages.

5.7.5 Early review of the effects of the randomised study treatments

Once the first one thousand participants have completed 6-months of follow-up, the net blood pressure and haemoglobin A_1c differences between the randomised groups will be reviewed. If the differences between randomised groups are insufficient to ensure an average difference in blood pressure of at least 6 mmHg systolic and an average difference in haemoglobin A_1c of at least 1% during follow-up, a recommendation may be made by the study Management Committee to alter the study treatment protocol or treatment titration protocol. Blood pressure and haemoglobin A_1c levels will continue to be monitored through out the course of the trial. The effects of treatment on all other outcomes will remain blinded until the completion of follow-up.

5.7.6 Interim monitoring of outcome

At regular intervals during follow-up, an independent Data and Safety Monitoring Committee will review data on deaths and major non-fatal macrovascular and microvascular events. The exact terms of reference for this committee will be established by its members in consultation with members of the study Management Committee. It is likely, however, that the terms adopted will be similar to those used in other large randomised trials such as PROGRESS (Perindopril Protection Against Recurrent Stroke Study). On this basis, the Data Monitoring Committee would be charged with informing the co-principal investigators if in their view, the randomised comparisons in ADVANCE have provided **both** (a) "proof beyond reasonable doubt" that for all, or for some specific types, of participant, treatment is clearly indicated or clearly contraindicated in terms of a net difference in all-cause mortality, **and** (b) evidence that might reasonably be expected to influence materially the participant management of many clinicians who are already aware of any other main trial results.

5.8 INDEMNITY

One of the study sponsors (Institut de Recherches Internationales Servier) shall at all times indemnify the study investigators and their staff from claims that may be made against them for any injury sustained by a study participant as a consequence of effects of the drugs used in the study in accordance with this protocol. This indemnity will be outlined in detail in the agreement between the International Coordinating Centre and the Local Clinical Centre (or Regional Coordinating Centre for Canada and China) and/or in a separate letter provided to the Local Clinical Centre by Servier.

5.9 PUBLICATIONS AND REPORTS

Publication of the main reports from the study will be in the name of the research group, with each individual study investigator named personally at the end of the report. Draft copies of publications will be provided to the Institut de Recherches Internationales Servier for review prior to submission of the manuscripts for publication but full editorial control will reside with the study Management Committee. The International Coordinating Centre will assist the Institut de Recherches Internationales Servier in the preparation of a study report that may be used in submissions to regulatory authorities.

5.10 FUNDING

ADVANCE is funded by a grant from the Institut de Recherches Internationales Servier. The study was initiated and designed by the investigators, independently of Servier and the data will be collected, analysed and published independent of Servier.

5.11 TIMELINE

Sep 2000 - May 2001	Centre recruitment, materials development, pilot testing, staff training
Jun 2001 - Mar 2003	Participant recruitment
Jun 2001 - Jun 2007	Participant follow-up and treatment with perindopril-indapamide or placebo
Jun 2001 – Dec 2007	Participant follow-up and treatment with gliclazide MR-based intensive glucose care or standard guidelines-based therapy. The Management Committee, on the advice of the Data and Safety Monitoring Committee, may recommend a different time for termination of participant treatment and follow-up.
Jun 2007 - Jul 2008	Statistical analysis and preparation of main results
Aug 2007 onwards	Dissemination of main results

5.12 ADMINISTRATIVE CLAUSES

The administrative clauses relating to this protocol are covered by the Agreement between the Local Clinical Centre or Regional Coordinating Centre and the International Coordinating Centre.

6. REFERENCES

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7. APPENDICES

Appendix 1 Information for consent of participants

The consent sought will comply with recommendations of the ICH guidelines for Good Clinical Research Practice, the Declaration of Helsinki and all relevant local, regional and national requirements as specified by the responsible ethics committee. This will include consent to collect a sample of blood for long-term (indefinite) deep frozen storage for the conduct of analyses on DNA and the components of blood plasma and blood serum. It will be stated that the exact analyses of the plasma and serum to be conducted are not yet known but the objective of the analyses will be to help determine the association between components of plasma and serum and the risk of various diseases, including but not limited to complications of diabetes. Individual results of the analyses will not be made available to either the study participant or any other party.

Each Local Clinical Centre will use the following sample Consent Form and Participant Information as a basis for the preparation of the consent form and participant information sheet required by their local ethics committee. The consent form and participant information sheet used at the Local Clinical Centre should comply with recommendations of the ICH Guidelines for Good Clinical Research Practice and any applicable local regulations. Where required, the Regional Coordinating Centres will assist with the preparation of the consent form and participant information sheet.

Participant Information Leaflet

Version 3 dated 30 November 2005
(Please give one copy to the participant and keep a copy for the Investigator)

Information for consent of participants: Version 3 dated 30 November 2005 from the ADVANCE International Protocol Amendment 1 dated 30 November 2005.

Investigator: Hospital: Telephone No.:

Study Title: ADVANCE - a factorial randomised controlled trial of blood pressure lowering with a fixed low-dose perindopril-indapamide combination and intensive glucose control with a modified-release gliclazide (gliclazide MR)-based regimen for the prevention of vascular disease among high risk individuals with type 2 diabetes mellitus

Study explanation
You are invited to take part in a study of two treatments that may be helpful in preventing heart disease, stroke, kidney disease and eye disease in individuals with adult onset diabetes. Your participation is entirely voluntary (your choice). You do not have to take part in this study. If you choose not to take part, your care or future treatment will not be affected. If you agree to take part, you are free to withdraw from the study at any time, without having to give a reason. Withdrawing at any time will in no way affect your future health care. To help you make your decision please read this information sheet. You may take as much time as you like to consider whether or not to take part. If you require an interpreter, this can be arranged. You will be encouraged to **ask questions** at all times during the study. If you have a problem or have more questions about the study, you can call 'study nurse' or 'study doctor' 'at any time on 'tel no …….'

The aim of the project is to find out whether more intensive control of blood pressure and blood glucose will prevent the development of new or worsening cardiovascular, eye or kidney disease among individuals with diabetes. A total of 10,000 participants across the world will take part in this study.

The two study medications under investigation are (1) a perindopril-indapamide combination tablet and (2) gliclazide MR. Both the study treatments have been used for many years in slightly different formulations and with slightly different aims. The use of these treatments in this study is different because the aim is to control blood pressure and blood glucose more tightly and because the treatments used in this study are in different formulations to those that have been most widely used to date. First, perindopril and indapamide are usually prescribed as two separate tablets. The combination tablet (perindopril-indapamide) used in this study has been developed to try and make a more effective treatment for blood pressure in one tablet. Second, the gliclazide treatment used in this study has been developed to release slowly throughout the day to try and provide good control of blood glucose levels throughout the whole day with the requirement only to take tablet(s) in the morning.

During the first 6 weeks, you will receive 1 tablet of the perindopril-indapamide combination daily. Once the first six weeks has been successfully completed, you will be randomly allocated (like the toss of a coin) to receive one of the four following treatments strategies for an average of 5.5 years:

1. The perindopril-indapamide combination that you received during the first 6 weeks and an intensive glucose control program (with treatment based on gliclazide MR) *or*
2. The perindopril-indapamide combination that you received during the first 6 weeks and your usual glucose control program *or*
3. A placebo for perindopril–indapamide (without pharmacological activity i.e. 'dummy' tablets) and an intensive glucose control program (with treatment based on gliclazide MR) *or*
4. A placebo for perindopril–indapamide (without pharmacological activity i.e. 'dummy' tablets) and your usual glucose control program

Neither you, nor your study doctor/nurse will know beforehand which of the four treatment groups you will be assigned to. Furthermore, once you are assigned to a group, you and your doctor will not know whether you have been allocated to the perindopril-indapamide combination or the matching placebo. However, both you and your doctor will know whether you have been allocated to the intensive glucose control regimen or to continue with your usual diabetes treatment.

As with all medication, there are **possible risks** that the study drug may cause side effects. These are generally mild and infrequent, and may be resolved immediately by reducing or stopping the treatment, but can include the following: cough, headache, skin rash, stomach pain, cramps, dizziness and nausea with perindopril; dry mouth, nausea, dizziness, constipation, low serum potassium with indapamide; dizziness, gastrointestinal disturbance (e.g. nausea, constipation or diarrhoea), hypoglycaemia (usually characterised by sweating, pallor, intense hunger, feeling unwell and other symptoms that your doctor will go through at the start of the study), skin conditions and abnormal blood and liver function tests with gliclazide MR. During the study, blood will be collected on a number of occasions and this may be associated with some bruising, discomfort, and local irritation.

The results obtained from the study may or may not be of **direct benefit** to your medical management. As with many clinical research projects, much of the benefit is for patients in the future. However some benefit may be derived from the increased visits to the study doctor, which are required by the study.

During the study
If you agree to participate, you will be seen at the beginning of the study on two occasions, prior to randomisation and at the randomisation visit. After randomisation, the schedule of visits will be different in the two different glucose control groups. Those assigned to the intensive glucose lowering regimen will be seen every three months and at 2 weeks, one month, 2 months and four months. Those assigned to the usual glucose control program will be seen every 6 months with additional visits at 3 months and 4 months. The mean follow-up of 5.5 years for the blood pressure part of the study will result in an average of 29 visits for each person assigned to the intensive glucose control group and 16 visits for each person assigned to the usual glucose control group. The mean follow-up of 6.0 years for the glucose control part of the study will result in an average of 31 visits for each person assigned to the intensive glucose control group and 18 visits for each person assigned to the usual glucose control group. At each visit you will be requested to return any unused tablets and new tablets will be provided to you.

Tests and assessments, which will occur during the visits above include: the collection of blood samples, measurement of blood pressure, weight and height, completion of quality of life questionnaires, giving details about your medical and diabetic history, assessment of your memory, testing of your vision, urine tests and the recording of ECGs (heart tracings). In addition, a sample of blood will be collected at the first visit for long-term (indefinite) deep frozen storage for the conduct of analyses on DNA and the components of blood plasma and blood serum. The exact analyses of the plasma and serum to be conducted are not yet known but the objective of the analyses will be to help discover the association between components of plasma and serum and the risk of various diseases, including but not limited to complications of diabetes. The individual results of the analyses will not be made available either to you or any other party.

If any injury is suffered as a result of the administration of the study medication or the performance of any medical procedures required by the study protocol, your 'study nurse' or 'study doctor' must be promptly informed on 'tel no'. Medical care will be made available to treat such injuries.

Your involvement in this project may be terminated at any time if you or your doctor feels that it is not in your best interest to continue, you do not wish to continue, or if you do not comply with the study procedures.

This study is supported by two sponsors, The George Institute for International Health based at the University of Sydney in Australia (Sydney, Australia) and Institut de Recherches Internationales Servier (Courbevoie, France). The sponsors will ensure that all study treatments are provided to you free of charge and have taken out an insurance policy to provide indemnity in the event of injuries relating to the study procedures. A third sponsor, Prognomix Inc., based at the University of Montreal (Montreal, Canada) will provide support for the analyses on DNA.

The participants in this study have a right to privacy and all information that is collected during this study is **strictly confidential.** However, the study monitors and the health authorities may need to examine your medical records to confirm the validity of the data collected. This will be done only to check the accuracy of the information collected for the study and the information will remain confidential. Case report forms and other medical records that do not identify you by name will be sent to the International Data Coordinating Centre. The data from the study will be **stored for at least 15 years** on case record forms and on computer disk. It will then be destroyed by shredding and erasure.

The **Ethics Committee of** …… has approved this information consent

Participant to initial this page _____	Page 2 of 3

Consent Form

(Please give one copy to the participant and keep a copy for the Investigator)

Information for consent of participants: Version 3 dated 30 November 2005 from the ADVANCE International Protocol Amendment 1 dated 30 November 2005

Study Title: ADVANCE - a factorial randomised controlled trial of blood pressure lowering with a fixed low-dose perindopril-indapamide combination and intensive glucose control with a modified-release gliclazide (gliclazide MR)-based regimen for the prevention of vascular disease among high risk individuals with type 2 diabetes mellitus

Participant:

Mr/Mrs/Miss (first and last name) : ……...

Address (street, suburb/town, state & postcode): ……..

……

- I have read the patient information sheet (Version 3 dated 30 November 2005) and understand the changes that have been made.
- I feel free to accept or refuse to participate at this study
- I have had a chance to ask questions and all of my questions have been answered to my satisfaction
- I have been given and I understand the information on the ADVANCE study concerning its nature, purpose, and duration as well as the procedures involved in the study, including any known or expected inconvenience, risk, discomfort, or potential side effects and of their implications as far as they are currently known by the researchers.
- My medical data are strictly confidential and I authorize their consultation only by persons involved in the research, identified by the sponsor or Health Authorities.
- By signing this form, I give my free and informed consent to take part in this study as outlined in the information sheet and this consent form. I have been given a copy of this consent form. By signing this form I have not given up my legal rights.

Printed name of participant:

Signature of participant: **Date:**

Printed name of legal representative (if applicable):

Signature of legal representative (if applicable): **Date:**

Printed name of investigator

Signature of investigator: **Date:**

Appendix 2 Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. (See footnote)
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. (See footnote)
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Note: **Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Note: **Note of clarification on paragraph 30 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

Appendix 3 Perindopril-indapamide fixed low dose combination

Information provided by Institut de Recherches Internationales Servier

The rationale for combining medications that lower blood pressure by different mechanisms is the expectation of enhanced efficacy related to the impact on different components on the cardiovascular system.[1] In particular, additional blood pressure-lowering effects might be produced by attenuation of the counter-regulatory mechanisms that are triggered whenever pharmacological intervention is initiated and that tend to blunt the drug-induced blood pressure reduction.[2] Another advantage of this approach is the minimization of dose-dependent adverse effects.[3] Additionally, the use of a fixed combination reduces the number of drugs taken by each participant, which may be particularly important for diabetic patients who frequently take a large number of drugs. The low dose combination of perindopril 2 mg and indapamide 0.625 mg have been shown to provide sustained efficacy (in reducing blood pressure) and safety in short and long term studies.[4,5] Synergistic properties of the two components have been demonstrated in studies of the correction of endothelial dysfunction.[6] Similar properties have been observed in the microcirculation.[7] Since endothelial and microcirculatory alterations are frequently observed in diabetes, these particular properties of the perindopril-indapamide fixed low dose combination may be of relevance in ADVANCE.

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5. Morgan T. Data on file
6. Hayakawa H, Coffee K, Raij L. Endothelial dysfunction and cardiorenal injury in experimental salt-sensitive hypertension. Effects of antihypertensive therapy. Circulation. 1997;96:2407-2413.
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Appendix 4 Modified-release gliclazide

Information provided by Institut de Recherches Internationales Servier

Sulfonylureas are widely prescribed oral antidiabetic agents, and once-daily administration is associated with significantly improved compliance.[1] Trials of the once-daily sulfonylurea, Diamicron MR® (gliclazide MR) in various populations have produced evidence of sustained reductions in fasting blood glucose and haemoglobin A_1c. In previously untreated patients, a reduction in haemoglobin A_1c of about 1% was observed at the end of 10 months' treatment. It was demonstrated during this period that the efficacy of Diamicron MR and Diamicron (current formulation) is equivalent in a large cohort. Episodes with symptoms suggesting hypoglycaemia on Diamicron MR were similar to those recorded on Diamicron and showed no excess in the elderly or those with mild to moderate renal insufficiency. Diamicron MR® is selective for the β-cell sulfonylurea receptor, without evidence of interaction with the cardiovascular K_{ATP} channels at any therapeutic concentration.[2] Diamicron MR® is well tolerated[3] and some evidence suggests additional potentially beneficial effects on oxidative stress, monocyte adhesion, platelet reactivity and endothelial function.[4,5]

1. Paes A, Bakker A, Soe-Angie C. Impact of dose frequency on patient compliance. Diabetes Care 1997;20:1512-1517.
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3. Drouin P and the Diamicron MR study group. Diamicron MR is effective and well tolerated once-daily in type 2 diabetes: a double-blind, randomised, multinational study. J Diabetes Complications 2000;14:185-191.
4. O'Brien R, Luo M, Balazo N, Mercuri J. In vitro and in vivo antioxidant properties of gliclazide. J Diabetes Complications 2000; 14: 201-206.
5. Jennings P. Vascular benefit of gliclazide beyond glycaemic control. Metabolism 2000; 49: S17-S20.

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Appendix 5 Study Visit Schedule

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	FINAL[a]
Form	**A**	**B**	**C**	**D**	**E**	**E**	**F**	**G**	**H**	**J**	**K**	**J**	**L**	**J**	**M**	**J**	**L**	**J**	**K**	**J**	**L**	**J**	**M**	**J**	**L**	**J**	**K**	**J**	**L**	**J**	**M**	
Month	-1.5	-0.5	0	0.5	1	2	3	4	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	
Phase	Run-in		RA	Follow-up all participants (except visits 4, 5, 6, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30, which are for the IG only)																												
Signed informed consent	X																															
Assess Eligibility	X	X	X																													
Medical history	X																															
Lifestyle	X														X								X								X	X
Cognitive function	X														X								X								X	
Assess Disability	X														X								X								X	X
Quality of life (EuroQol)	X														X								X								X	X
Quality of life (SF-36)	S														S								S								S	S
Resource utilization	S														S								S								S	
BP and heart rate	X	X	X	IG	IG	IG	X	X	X		X		X		X		X		X		X		X		X		X		X		X	X
Weight	X								X		X		X		X		X		X		X		X		X		X		X		X	X
Visual acuity	X														X								X								X	X
Fundoscopy	X*														X								X								X	
Neuropathy/ limb ulceration	X														X								X								X	
ECG	X**														X								X								X	
Biochemistry	C	L						L			L				C				L				C				L				C	L
Blood glucose	X		X	IG	IG	IG	IG	IG	IG		IG		IG		X		IG		IG		IG		X		IG		IG		IG		X	X
Haemoglobin A1c	X				IG	IG	IG		X	IG	X	IG	IG	IG	X	IG	IG	IG	X	IG	IG	IG	X	IG	IG	IG	X	IG	IG	IG	X	X
Albumin:creatinine ratio	X**														X								X								X	X
Blood for long-term storage	X										RS																					
Serious adverse events		X	X	IG	IG	IG	X	X	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	X
Glucose Lowering Treatments	X		X						X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	X
Other Concomitant Treatments	X		X						X		X		X		X		X		X		X		X		X		X		X		X	X
Adherence			X	IG	IG	IG	X	X	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	IG	X	X
Tolerability of study drugs		X	X				X	X	X		X		X		X		X		X		X		X		X		X		X		X	X
Tablets perind-indap/placebo	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	***
Tablets gliclazide MR			IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	IG	***
Tablets perindopril 2mg	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	***

X = All patients
IG = Intensive Group
RA = Randomisation visit
a= for both end-of study visits

RS = Random Sample
L = Creatinine, Sodium and Potassium
C = Comprehensive blood biochemistry

S = Sample
* = Not required if assessment within last 6 months & results available
** = Not required if assessment within last 3 months & results available
***= if indicated in the opinion of the responsible investigator; at the first end-of-study visit only

Appendix 6 Blood pressure measurement

Blood pressure should be measured with the participant in a sitting position using an Omron or other non-invasive device, if an Omron is not available. Detailed information about the use of the Omron will be provided with the device.

When measuring blood pressure, particular care should be taken to:

- allow the participant to sit for several minutes in a quiet room before beginning blood pressure measurement
- use a cuff appropriate to arm width
- place the cuff at heart level
- take three measurements after 5 minutes rest, separated by at least 1 minute and ensure that the cuff is completely deflated following the first measurement
- record measurements 2 and 3 on the case record form

ADVANCE	**Appendix 7 - Form X** **Serious Adverse Events**	Registration Number _____ Date of birth _____ Patient Initials _____

Answer every main question. Answer every supplementary question (If Yes or If No) as indicated by arrows.
Tick boxes. Write numbers in spaces. Enter all dates as day/month/year.
Use codes provided where appropriate.
Enter * if data will never be available.
Complete as much information as possible and then send this form, do not wait for full information.
N.B. Each new hospital admission must be reported on a separate Form X

1. Details of Serious Adverse Event/Study outcome

Please describe all outcome events and SAEs occurring within an admission or within the same episode

	Specific diagnosis/procedure	**ICD Code** *(leave blank if not known)*	**Event code**	**Date of onset** Day	Month	Year	**Resolution code**	**Association code**
1.01	_____	____	__	__	__	____	__	__
1.02	_____	____	__	__	__	____	__	__
1.03	_____	____	__	__	__	____	__	__
1.04	_____	____	__	__	__	____	__	__

2. Heart Failure

yes no

2.01 [Y] [N] Diagnosis of heart failure being reported
2.02 If yes → [Y] [N] New diagnosis or NYHA class increased by one or more

3. Hospitalisation

yes no

3.01 [Y] [N] Admitted to hospital (completed formal admission procedures)
3.02 If yes → __ __ __ __ __ __ __ __ Date admitted to hospital
3.03 → __ __ __ __ __ __ __ __ Date discharged from hospital or date died in hospital (leave blank if still in hospital)

4. Death

yes no

4.01 [Y] [N] Did the patient die
4.02 If yes → __ __ __ __ __ __ __ __ Date of death
4.03 → [Y] [N] Autopsy performed

	Cause of death		**ICD Code** *(leave blank if not known)*
4.04	_____	Proximate/Immediate cause	_____
4.05	_____	Underlying cause	_____

5. Study treatment

5.01 |__|__| |__|__| |__|__|__|__| Date last dose of perindopril-indapamide/placebo taken before first event reported on this form

yes no
5.02 [Y] [N] Was dosage of perindopril-indapamide/placebo changed after first event reported on this form
5.03 If yes → |__| Number of tablets of perindopril-indapamide/placebo taken daily after first event reported on this form (enter 0 if study treatment stopped)
5.04 [Y] [N] Patient randomised to intensive glucose control
5.05 If yes → |__|__| |__|__| |__|__|__|__| Date last dose of gliclazide taken before first event reported on this form

yes no
5.06 [Y] [N] Was dosage of gliclazide changed after first event reported on this form
5.07 If yes → |__| Number of tablets of gliclazide taken daily after first event reported on this form (enter 0 if study treatment stopped)

6. Documentation for primary study outcomes and serious reactions to study drugs

yes no
6.01 [Y] [N] Is a primary study outcome (stroke, MI, CV death, nephropathy, eye disease) or a suspected serious reaction to study drug being reported

If Yes, Please mail copies of the relevant document(s) to the International Coordinating Centre. Remove patient name/address and label all pages with patient registration number and initials. N.B. Any serious reaction to study drug must be reported immediately

yes no (Indicate which documentation has been sent)

6.02 If yes → [Y] [N] ECG
6.03 → [Y] [N] Cardiac enzymes
6.04 → [Y] [N] Other laboratory reports
6.05 → [Y] [N] CT report and/or MRI report
6.06 → [Y] [N] Clinical notes (admission notes, discharge summary)
6.07 → [Y] [N] Ophthalmologist report (e.g. fundoscopy, retinal photography, visual acuity)
6.08 → [Y] [N] Nephrologist report (e.g. albumin:creatinine ratio, 24 hour urine, creatinine)
6.09 → [Y] [N] Autopsy report
6.10 → [Y] [N] Death certificate
6.11 → [Y] [N] Other relevant documentation

7. Signature of investigator

Name |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__| Signature |_____|
Date signed |__|__| |__|__| |__|__|__|__|

Appendix 7 – Form X Codes

Event Code (choose the code that best describes the event)

1. Death
2. Life Threatening Event
3. Permanent or substantial disability
4. Hospitalisation or prolongation of hospitalisation
5. Cancer
6. Medically Important
7. Congenital abnormality
8. Overdose

Association Code

1. Not a serious suspected study drug reaction
2. Suspected serious adverse drug reaction to perindopril
3. Suspected serious adverse drug reaction to indapamide
4. Suspected serious adverse drug reaction to perindopril-indapamide combination (unable to determine whether the reaction was due to the perindopril component or the indapamide component)
5. Suspected serious adverse drug reaction to gliclazide
6. Serious reaction to non-study drug
7. Serious reaction to study procedure

Resolution Code (in the opinion of the investigator)

1. Recovered
2. Improved
3. Unchanged
4. Sustained lasting damage
5. Worsened
6. Death