



A reliable assessment of the efficacy and safety of donepezil and aspirin in Alzheimer's disease

PROTOCOL

Donepezil (Aricept) is one of an expanding group of acetylcholinesterase inhibitors which enhance neurotransmitter levels in the central nervous system. Three randomised placebo-controlled trials, involving 1900 people with mild to moderate 'probable Alzheimer's disease', have established that donepezil can improve performance in cognitive function tests. The effects are ameliorative with no evidence that the drug reverses the underlying disease process. Effects of donepezil on severity of disease are less clear and no robust effects on disability or quality of life – of patient or carer - have yet been shown. The drug appears to be safe in the short to medium term.

Importantly, the effectiveness of donepezil in routine clinical practice remains uncertain. Despite this, donepezil was licensed in the UK in March 1997. So far, however, it has not been widely prescribed because of concerns that the moderate improvements in cognitive function tests (an average difference between donepezil and placebo of less than 3 points on a scale of 70) may not necessarily translate into worthwhile clinical and social benefit. It is also not possible, on present evidence, to predict which type of patient is more likely to benefit, and it is not known how long treatment should be continued, or what dose of donepezil is optimal. What is needed is much better evidence on the effects of donepezil on non-cognitive symptoms, functioning in daily life, level of dependency, well-being of carers, and need for institutionalisation to help guide future practice.

AD2000 is a large, simple, 'real life' trial that aims to produce reliable evidence on the value of donepezil in routine practice by randomising 3,000 people with mild or moderate Alzheimer's disease to receive either donepezil (5mg) or placebo. After 12 weeks treatment patients will be re-assessed and then continue for another year either with the same treatment (i.e. donepezil or placebo), or crossed over to the alternate treatment, again at random. (Thus three out of four patients receive at least 12 weeks of donepezil). Those allocated donepezil from week 13 onwards will be sub-randomised between 5mg and 10mg daily. To investigate whether aspirin delays progression of dementia, patients without a positive indication for, or definite contra-indication against, aspirin will be further randomised to receive daily aspirin or to avoid aspirin.

To make large-scale recruitment feasible, and to maximise the clinical relevance of the eventual findings, the trial is designed to fit in with routine practice with a minimum of extra tests and investigations over those that would be required routinely. During the study the accumulating data – from AD2000 and other relevant studies - will be regularly reviewed by an independent data-monitoring committee who will advise the trial Steering Group if clear evidence of worthwhile benefit, for all or certain classes of patient, emerges before the scheduled recruitment is complete. It is anticipated that recruitment will take about a year and, thus, that the first results of AD2000 will become available by the year 2000.

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All who drink of this remedy recover in a short time, except those whom it does not help, who all die. Therefore it is obvious that it fails only in incurable cases.

Galen, AD 180

Until the mid-1930s, therapeutic medicine had advanced only slowly and very few effective remedies had been introduced. In the half century that has followed, useless remedies that filled dispensaries throughout the world, which were the stock-in-trade of physicians, have now largely disappeared from the developed world. They have been replaced by a smaller number of effective remedies, and recommendations for healthy living, some of which, it must be admitted, have been introduced into routine practice only slowly. We now, however, have techniques [very large randomised trials] for ensuring that the true effects of new therapies are quickly discovered.

Sir Richard Doll, Darwin Lecture, 1990.

1. CHOLINERGIC AGENTS: WHICH PATIENTS, AND FOR HOW LONG?

Donepezil improves cognitive function in selected patients with Alzheimer's disease

Dementia is a chronic progressive organic mental disorder in which there is disturbance of multiple higher cortical functions including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgement. Alzheimer's disease (AD) is the commonest cause of dementia and is characterised by degeneration of specific nerve cells, presence of neuritic plaques, and neurofibrillary tangles. Definitive diagnosis of AD requires demonstration of these pathological features in brain tissue, although in the vast majority of cases diagnosis is made on clinical grounds alone.

There are an estimated 650,000 people with dementia living in the UK, of whom about 400,000 have Alzheimer's disease¹. Incidence is highly age dependent affecting 5% of those aged over 65, and 25% of those over the age of 85². Rates of progression of Alzheimer's disease vary considerably and are difficult to predict³⁻⁵. Incidence has been stable over the past two decades⁶, although demographic change will result in an increase in prevalence, and an increase in the already considerable cost of over £1.5 billion per year that AD imposes on the UK economy⁷.

Donepezil, a piperidine, is a new drug treatment for AD which has recently been licensed in the UK. Donepezil acts by inhibiting the enzyme responsible for metabolising acetylcholine, thereby enhancing neurotransmitter levels. Further effects on other elements in brain metabolism may also be relevant, although these have not been studied in detail. Donepezil is a symptomatic treatment. There is no empirical evidence that the drug affects the underlying disease process and benefits are likely to reduce over time as cholinergic neurones degenerate.

There have been four randomised controlled trials of donepezil, involving a total of 1900 highly selected patients with mild to moderate 'probable'. As of June 1998, an early dose-finding study⁸, and the two US Phase III studies⁹⁻¹⁰ had been published in full, and partial details are available for the multinational study¹¹. The treatment periods lasted between 12 and 24 weeks. The primary outcome measures were the cognitive subscale of the Alzheimer's Disease Assessment Scale¹² (ADAS-cog) and the Clinical Global Impression of Change¹³ (CGIC) or Clinician Interview Based Impression of Change¹⁴ (CIBIC Plus).

Donepezil treatment at doses of 5-10mg/day was well tolerated¹⁵ and moderately improved cognitive function, as measured by ADAS-cog scores⁹⁻¹¹. After withdrawal of donepezil treatment, cognitive status declined to placebo group level. Statistically significant improvements in cognitive function from baseline were also seen in the placebo groups in the early weeks of these trials. This may be due to a placebo effect and/or a learning effect.

Information on longer term responses to donepezil is available from the uncontrolled (and hence unreliable) A202 cohort study¹⁶, which also had a high drop out rate (68% by two years). After the initial 12 week comparison, all patients received a two week washout followed by open label donepezil. A second improvement phase was seen after this which may be due to patients on placebo being transferred to donepezil and/or dose being escalated. Thereafter, there was a gradual decline in cognitive function. The absence of a control group in this two year study prevents a direct comparison of ongoing rate of decline but the overall rate (6.6 points per year) was broadly similar to that among placebo-treated patients earlier in the study, and that among historical controls¹⁷, suggesting that medium term decline is not prevented.

ADAS-cog scores showed greater difference over placebo in the groups receiving higher doses of donepezil⁹. In the US 24 weeks study thirty-eight per cent of patients in the 5mg group, completing treatment, 53% of those in the 10mg group, and 27% of the placebo group showed improvement of at least 4 ADAS-cog points, although pairwise comparisons of effect between different doses are not statistically significant. Pharmacological considerations suggest that there may not be a big difference in effectiveness between 5mgs and 10mgs. Rogers *et al*⁸ reported that a plateau of acetylcholinesterase inhibitory activity is reached on 5mg per day, corresponding to between 77% and 84% of enzyme inhibition - i.e. efficacy approaching the theoretical limit based on the underlying function of the drug. Side-effects are, however, dose-dependent (see below).

No clear effects on severity of disease, or evidence of effectiveness in routine clinical practice

Clinical change - as assessed by the CGIC or CIBIC scales - compared to baseline showed a small statistically significant improvement from donepezil over placebo in the 12 and 24 week RCTs⁹⁻¹¹. In the 24-week RCTs, a positive result is also reported for CDR-SB scores, an accepted measure of severity in AD¹⁸. In the US 24 week trial, the placebo group worsened by, on average, 0.58 points compared to very small improvements in the 5mg (-0.01 points) and 10mg (-0.02 points) groups ($P < 0.001$)⁹. Data on longer term changes in severity are available from the cohort study¹⁶ - CDR-SB scores improved during the 12 week of treatment in the RCTs, followed by a stable period slightly worse than baseline of around three months and then gradual worsening, equivalent to a 1.8 CDR-SB point increase per year compared to an expected 2.4 based on previous reports.

The clinical relevance of these results is not stated and in some cases may be small. Benefits measured by clinicians on the CIBIC/CGIC scales are difficult to interpret. The scales have good face validity but lack standardisation and the memory items may carry undue weight¹⁴. The 0.6 point difference in CDR-SB scores compared to controls seen in the 24-week US trial may also be partly due to cognitive improvement. No clear benefits of donepezil are reported on quality of life, non-cognitive symptoms, basic activities of daily living, well-being of carers, or economic endpoints in any of the information currently available.

Moreover, the patients in the trials were a highly selected group with a well established diagnosis, made by experienced specialists and usually with CT support and neuropsychological investigation. It is estimated that only about 10-15% of the patients seen in a typical outpatient department would have been eligible for these trials. The risks of greater side effects in more representative people with AD, many of whom have co-morbidity and may already be on other drugs, may outweigh the benefits and make it difficult to conclude on overall effectiveness.

Side-effects of donepezil

Side-effects experienced by participants in the clinical trials of donepezil were, on the whole, not serious, but showed clear dose dependency¹⁵. Gastrointestinal symptoms were most commonly reported. Among 1,102 patients for whom data are available, 31% of those on treatment experienced gastrointestinal symptoms compared to 22% taking placebo. Diarrhoea (10% on treatment vs. 5% in controls) and nausea (11% on treatment vs. 6% in controls) predominated. These effects were more prevalent in the 10mg groups ($n = 315$), affecting 19% (nausea) and 15% (diarrhoea). Vomiting was also experienced by a larger proportion of patients on 10mg (but not others) than controls (8% vs. 3%). A rate of adverse events comparable to that with 5mg was seen when dose was escalated from 5mg to 10mg at six weeks rather than after one week¹⁵.

Nervous system symptoms were also experienced by a greater proportion of treatment subjects than controls (32% vs. 25%)¹⁵. This effect was again principally due to the excess of symptoms appearing in the 10mg treatment group (38%), in particular insomnia (14% vs. 6% in controls)¹⁵. Dizziness, which might be predicted with cholinomimetic treatment, was not shown more frequently in the treatment groups than in controls. Although several patients in the open-label cohort study experienced syncope or falls, the absence of a control group prevents evaluation of the role of donepezil in these events. A significant decrease in blood pressure was shown in patients in the 24 week trial, although the mean change of -3.45 mm Hg was not considered clinically significant.

Symptoms resulting in withdrawal from treatment were experienced by 9% of those on donepezil and 5% of controls. Patients receiving 10mg donepezil were more likely to discontinue treatment than those on lower doses: 6% for the <10mg groups vs. 13% for the 10mg groups.

Cost-effectiveness of donepezil

The great bulk of the £1.5 billion per year costs of AD are for residential and NHS in-patient care. There is, as yet, no evidence for any likely reduction in NHS or Local Authority Social Service (LASS) costs from use of donepezil for Alzheimer's disease. It is possible that an improvement in clinical condition due to donepezil could reduce costs in any one year by delaying the need for residential care. Conversely, earlier contact with services, by people with dementia from all causes, as a result of public knowledge about availability of treatment may increase NHS costs. The drug cost of donepezil is £891/year at 5mgs and £1248/year at 10mgs. This is about equivalent to the cost of four weeks institutional care. The use of donepezil could be broadly cost-neutral, or cost-beneficial, if the increased costs of the drug were offset by reduced costs due to delayed care requirements.

Estimating the likely duration of donepezil treatment, and therefore total drug costs, is difficult. There is a theoretical limit to beneficial effects through loss of cholinergic neurones, and a pragmatic limit to treatment based on the indications for donepezil (i.e. progression to severe dementia). Trial data suggest that, in the first few months, withdrawal of treatment leads to rapid loss of early gains in cognitive function. How long this effect would be shown is unknown. If the effectiveness of donepezil

does diminish with longer use then treatment duration should be limited. In practice, in the absence of evidence-based criteria for withdrawal, treatment may become lifelong. Survival of Alzheimer's disease patients is, however, difficult to predict¹⁹⁻²⁰. Patients in AD2000 will be followed up long-term to obtain better data on this.

The important costs arising from Alzheimer's disease are borne by informal caregivers, the NHS, residential care services, social services and voluntary agencies. There is no evidence to support claims of savings in these sectors from the use of donepezil. Comprehensive information is lacking from most agencies on the use of services by people with Alzheimer's disease and on the economic and social costs falling to informal caregivers. The AD2000 study will collect data which will allow the economic effects of donepezil to be appraised.

The need for AD2000: a new, much larger randomised trial

Previous trials of donepezil have included a highly-selected group of patients with mild to moderate 'probable' Alzheimer's disease²¹, screening out patients with any evidence of vascular dementia or with concomitant diseases. As a result, it is unclear whether more clinically representative patients benefit from donepezil. Moreover, the lack of full publication of the trial data is unsatisfactory. Precision of the estimates of treatment effect in the unpublished trials is currently unknown. Not all of the available analyses are performed on an intention to treat basis, methods of randomisation and concealment are not reported, and not all patients who entered the trial are accounted for at trial completion (e.g. CGIC scores in Rogers et al⁸.) These are all potential sources of bias²².

There is also marked heterogeneity of response to donepezil, but no information is available to help predict which patients would benefit most. Cognitive response after 12 weeks treatment is sometimes used to determine whether further treatment is indicated, but it is unclear where the cut-off for this lies. Other potentially important variables include severity of disease, Apolipoprotein E genotype, presence of Lewy body and or vascular pathology, all of which may affect prognosis and treatment response. A further area of uncertainty regards interaction with other drugs used in the elderly (e.g. phenothiazines). Concomitant psycho-active medication was an exclusion criterion in the published trials of donepezil. Two small studies suggest that there is no adverse pharmacodynamic interaction with digoxin²³ or with warfarin²⁴ but this needs to be confirmed empirically.

Donepezil is a promising new treatment for Alzheimer's disease but no reliable information on its effect on socially and economically important outcomes such as institutionalisation, dependency²⁵, caregiver's psychological well-being and time input²⁶ is available. In particular, no delays in disease progression or the need for institutionalisation have been established.

So, although in total some 1900 patients have been randomised in previous studies of donepezil, and 1100 patients have been randomised between high and low-dose donepezil, important questions about the efficacy and best use of the drug remain unanswered. Independent reviews of the available evidence on donepezil have recommended that the drug should not be prescribed on the NHS until better, and fuller, evidence of worthwhile efficacy becomes available²⁷⁻²⁹. Partly because of these doubts, few health authorities have agreed to fund the drug and prescribing has been described as a health care lottery³⁰. **AD2000** aims to randomise a further 3000 patients between donepezil and placebo and 1500 between the two different donepezil doses and thereby to produce much more reliable information on the effects of donepezil on clinically and socially important outcomes to help inform future practice.

Other cholinergic agents

Donepezil is just one of an expanding group of acetyl-cholinesterase inhibitors. The best researched of the other drugs is Exelon, with 3300 patients randomised in four placebo controlled 6-month studies. Preliminary results from these studies suggest a broadly similar effect on cognitive function as donepezil. A statistically significant improvement in activities of daily living is reported when all Exelon studies are combined³¹. However, it is again unclear how clinically relevant this is, what impact it may have on the quality of life of patient and carer, caregiver time or economic endpoints. No randomised evaluation of long-term efficacy has been undertaken and a full publication of the short-term outcome data is not available. Other cholinesterase inhibitors are at various stages of development but these too are likely to be of broadly comparable efficacy to donepezil. Thus, although donepezil may eventually be superseded by similar drugs - which have less side-effects or which cost less - the results from AD2000 will be of direct relevance to the best use of these new agents.

Non-steroidal anti-inflammatory drugs: aspirin

The importance of cerebrovascular disease in Alzheimer's disease has been highlighted in recent studies with considerable overlap between dementia of the Alzheimer's type and vascular dementia. This suggests that aspirin – which is known to reduce the risk of stroke - might produce moderate, but potentially worthwhile benefits in dementia. NSAIDs are reported in several observational studies to be associated with less Alzheimer's disease and with slower symptom progression³². One small randomised trial of short term aspirin has reported a significant improvement in cognitive function in patients with multi-infarct dementia³³ taking aspirin (325mg/day) for three years, but the methodology used was flawed. The AD2000 trial provides an excellent opportunity to investigate whether aspirin really does delay disease progression. Patients not already taking aspirin, and without known ischaemic heart disease or other positive indication for aspirin, will, therefore, be sub-randomised between aspirin and open control, using paracetamol for analgesia as appropriate. It is recommended that enteric-coated aspirin should be used at a dose of 75 mg/day – which is sufficient to achieve an anti-platelet effect – and which will minimise the risk of side-effects.

Genetic Studies

Dementia of Alzheimer's Type is a complex multigenic disorder³⁴. Three relatively rare, familial, early-onset forms have been identified to date (APP and the presenilins PS-1 and PS-2). However, in the majority of Alzheimer's disease it is believed that a combination of genes of more modest effect together with environmental factors determine disease susceptibility. The ϵ 4 variant of the Apolipoprotein E (ApoE) gene is a potent *susceptibility* gene for early and late onset Alzheimer's disease and a number of other potential susceptibility genes have been implicated. Genotype may be predictive of treatment response. A small study of tacrine treatment of AD suggested that the presence of the ϵ 4 allele predicted poor response to this anti-cholinesterase drug³⁵. However, a preliminary report from a trial of the experimental drug S12024 suggested the opposite effect, that presence of the ApoE ϵ 4 allele predicted better outcome³⁶. These observations have enormous potential therapeutic implications for facilitating the targeting of therapies at sub-groups likely to derive most benefit from treatment, and require investigation in larger, independent samples. "Pharmacogenetics" may become an essential part of future management of Alzheimer's disease³⁷, and the genetic studies in the AD2000 trial will make a major contribution to this.

A 10ml venous blood sample will be obtained from each consenting patient at the time of recruitment and sent to the Molecular Psychiatry Laboratory at the University of Birmingham where DNA will be extracted. The blood tube and pre-addressed, pre-paid packaging will be provided as part of the AD2000 pack. Genotyping will be performed for the ApoE polymorphism and, as new information becomes available, for other genetic polymorphisms found to influence susceptibility to Alzheimer's disease. Genotype will be examined as a predictor variable for treatment outcome.

The blood and DNA samples will be identified within the laboratory by anonymous numerical code and will be stored in freezers within locked laboratories. All information will be strictly confidential. Participants will derive no personal benefit and no individual results will be made available. If important genotype-treatment interactions are identified, any requests for individual results would be re-directed through the normal Health Services channels (i.e. General Practitioner and, if appropriate, referral to specialist services).

2. OUTCOME MEASURES

The only reliably established benefit of donepezil is improved cognitive performance, as measured by ADAS-cog scores and MMSE. Although cognitive and functional status are correlated in Alzheimer's disease ($r = 0.5$ to 0.6)^{38,39} some authors have suggested that they represent distinct but parallel processes³⁹. Non-cognitive symptoms may bear a greater relationship to quality of life, particularly effects on carers⁴⁰. The ultimate measure of outcome must be functioning in daily life, which is usually assessed via carer rated activities of daily living (ADL) scales, and the psychological wellbeing of carers of dementia sufferers. The inability of the carer to cope with increasingly troublesome behavioural symptoms is often the precipitating factor that leads to the patient's transition to formal residential care⁴¹.

The two primary endpoints in AD2000, therefore, will be:

- Increase in disability as defined by **either** loss of two of four basic ADLs (i.e. dressing, eating, washing, and using the toilet) **and/or** loss of six of eleven instrumental ADLs (see below).

- The requirement for formal domiciliary or residential care

Secondary endpoints will be:

- Progress to severe cognitive disability (MMSE score <10)
- Activities of Daily Living (Bristol ADL Scale)
- Presence and severity of non-cognitive neuro-psychiatric symptoms (NPI)
- **Time spent by caregivers both formal and informal**
- Psychological well-being of the principal caregiver (GHQ-30 Scale)
- Death from Alzheimer's disease (ignoring deaths from other causes)
- Safety
- Compliance (numbers stopping treatment because of side-effects/lack of perceived effectiveness/other reason)

The outcome measures to be used in AD2000 are well validated and relatively quick and easy to administer.

Cognitive function: Mini-Mental State Examination

MMSE is a well established measure of cognitive function in elderly people. It shows good test-retest and inter-rater reliability and performs satisfactorily against more detailed measures of cognitive function. The MMSE is more sensitive than alternative measures at milder levels of cognitive impairment but may be subject to bias from sociodemographic variability in subjects⁴². Levels of 10 to 26 correspond to mild to moderate cognitive impairment in dementia. A score below 10 represents severe disabling dementia and is a stable milestone from which patients rarely recover⁴³.

Cognitive function below 10 on MMSE is used in the definition of the milestone endpoint of 'severe cognitive disability' but MMSE score is not an endpoint in itself. It will be used, however, to investigate whether change in MMSE score at 12 weeks can predict which patients do, and do not, benefit from continuing donepezil treatment.

Activities of daily living: Bristol ADL Scale

Many activities of daily living scales have proved to be insensitive to change in patients with dementia, others are hierarchical in nature classifying patients on whether they can complete increasingly difficult tasks without being sensitive to changes in performance in individual skills. Some scales have been designed to distinguish between normal and abnormal ageing rather than assess the wide range of ADL skills present in different stages of dementia. Individual items on behavioural questionnaires may not accurately reflect problems as identified by carers and may be totally inappropriate at times. The Bristol Activities of Daily Living Scale is a newer assessment that has been developed in an attempt to overcome some of these shortcomings⁴⁴ and will be used in **AD2000**.

Increase in disability

Increase in disability is defined as **either** loss of two of the four basic ADLs (i.e. progress from moderate to severe disability as assessed by the requirement for direct assistance with two of: eating, dressing, washing, and using the toilet) **and/or** loss of six of eleven instrumental ADLs (i.e. progress from mild to moderate disability as assessed by loss of ability to prepare food, to make a drink, to know the time, to know ones location, to hold a conversation, to use the telephone, to do housework/gardening, to do shopping, to manage finances, to participate in games/hobbies, and/or to use transport). Severe disability is defined as reaching stage d on the Bristol ADL Scale (Appendix D2) for questions 2, 5, and 6, and stage c for question 9. These represent a level of dependency that would require substantial increases in caregiver time with obvious social and economic consequences. This endpoint is closely related to the severe dependency definition used in the US Vitamin E/Selegiline Study⁴⁵, the 'complete dependency' level used by Stern et al²⁵, and is again a stable endpoint from which patients rarely recover⁴³. Moderate disability is a more relevant endpoint for patients with mild dementia few of whom would reach the severe disability level before several years. Moderate disability to perform instrumental ADLs is defined as reaching level 'd' on Bristol ADL questions 1,3,15, or 19; level 'e' or worse on questions 13,16,17,18, or 20; and level 'b' or worse on questions 12 or 14.

Burden on carers: care-givers time and psychological well-being

Carers of patients with dementia presenting to psychiatric services have been shown to have a high level of psychological morbidity⁴⁶ and depressive illness is common⁴⁷. Institutionalisation may have more to do with the attitudes and well-being of the carer than the impairment of dementia. This is related to the complex interaction of a number of factors including: problem behaviours arising from the patient, the care-giving relationship, attributional factors, and coping strategies⁴⁸. Carer depression has also been shown to be associated with abuse of the demented person⁴⁹. Interventions that successfully reduce the psychological morbidity of carers may delay institutionalisation⁵⁰ without increasing the use of health services by either patient or carer. Little work has gone into researching the effect of anticholinesterase prescription on carer attitudes, stress and psychological morbidity. Unpaid care-giver time has been shown to be sensitive to changes in cognitive function and may be another useful outcome measure in clinical trials in AD²⁶. In **AD2000**, a modified version of the Caregiver Activities Time Survey²⁶ is used to measure caregiver time, and the General Health Questionnaire (GHQ-30) scale has been chosen to detect psychiatric morbidity in carers. The answers are scored 0,0,1,1 (the 'GHQ' Scoring method) and a score of 5 and above indicates psychiatric morbidity. The GHQ is well validated, is sensitive to change, not unduly affected by physical symptoms, and is self-rated⁵¹.

Non-cognitive symptoms

Non-cognitive behavioural and psychiatric symptoms are risk factors for institutionalisation and alleviation of these symptoms might delay or prevent the need for residential care⁴⁰. The Neuropsychiatric Inventory (NPI)⁵² assesses twelve behavioural disturbances in dementia – using a screening strategy to save time. The NPI is reliable and valid and has been reported to be sensitive to the effects of Tacrine⁵³. A modified NPI – which can be administered by a nurse - is used in AD2000 to measure the caregiver's assessment of non-cognitive neuro-psychiatric symptoms.

Transition to formal domiciliary or residential care

Progression of Alzheimer's Disease leads to increased requirements for formal domiciliary or residential care as the limits of informal care are exceeded. Transitions to more intensive forms of care can be viewed both as outcome and as costs. Caregivers time and psychological well being, as noted above, will be measured as secondary outcomes. Changes in the costs associated with informal care, which are likely to be borne by spouses, family and other carers, will be obtained from carers, validated where possible by administrative data, and combined with a range of unit costs to estimate the total cost of informal care. The transitions to formal or paid inputs of care will impose costs either on the public sector or families. Public sector costs are likely to be borne initially by the NHS in terms of short term admissions (geriatrics, old age psychiatry), followed by individual needs assessment by the Local Authority Social Services Department, leading in turn to packages of domiciliary care and later, if and as appropriate, to placement in a residential care or nursing home. To the extent that donepezil delays these transitions, it may reduce costs. The economic evaluation will include both informal and formal costs, both those borne by the NHS and by LASS or privately by patients or their families. Fuller details of the economic evaluation are discussed elsewhere⁵⁴.

3. TRIAL DESIGN

The three fundamental questions being addressed in AD2000 are:

- **Does donepezil produce clinically and socially worthwhile benefits for typical UK patients with Alzheimer's disease?** This will be addressed by direct comparisons of outcome between donepezil and placebo allocated patients.
- **If so, how long do these benefits persist?** The size of treatment benefit will be assessed 12-weekly for 60 weeks to determine how long any benefits persist.
- **Can presentation characteristics, or response to 12 weeks treatment, predict which patients benefit?** Comparisons of the size of treatment effect within different subgroups, and between those with good, moderate and poor cognitive response to the first 12 weeks of donepezil, will provide evidence on this.

Large, simple trial: minimal extra investigations and data collection

To make really large-scale recruitment feasible, the **AD2000** trial is "streamlined" so as to impose minimal extra workload on participating clinicians, beyond that required to treat their patients. Multi-centre Research Ethics Committee approval has been obtained, which makes Local Research Ethics

Committee submission much easier. Trial drugs will be supplied to each participating centre in convenient treatment packs, identified only by code numbers in order to "blind" the study. The important prognostic information will be collected at the telephone randomisation, so there is no entry form. Thereafter, only the minimum data needed to evaluate the effects of donepezil on the study endpoints are collected. Follow-up visits need not involve the consultant. A nurse can administer the cognitive and neuro-psychiatric assessment, and the carer completes a questionnaire assessing activities of daily living (disability), care-time input, and the carer's psychological well-being. The follow-up assessments are undertaken two weeks before completing each 12-week course of donepezil/placebo. Six weeks after completion of treatment, there will be a further re-assessment. Thereafter, there is just one annual follow-up to the patient's carer, requesting details of the patient's current status. This information will be supplemented by the use of national mortality records to ensure long-term follow-up. Regular newsletters will keep participants informed of trial progress, and regular meetings of collaborators will be held to address any problems encountered in the conduct of the study.

Randomised comparison of donepezil versus placebo: eligibility based on "uncertainty"

There is disagreement on the clinical relevance of the effects of donepezil on cognition. At one end of the spectrum, some clinicians (and most UK Health Authorities) consider that the existing evidence on the cost-effectiveness of donepezil is insufficient to justify large scale use of NHS resources on the drug. Such doctors, who are sceptical about donepezil, might consider using it only for patients with mild to moderate 'probable' Alzheimer's disease (as studied in the clinical trials) - since these are thought to be most likely to respond. Other clinicians believe that such patients should be offered donepezil, on existing evidence, but are uncertain whether other patients (eg. those with mixed Alzheimer's disease) would benefit. Still others would wish to consider possible use of donepezil for all of their suitable patients. The level of disability of a patient is also a potential determinant of the appropriateness of donepezil treatment – and, again, there are divergent opinions.

In view of these considerations, **AD2000** adopts a pragmatic approach and eligibility is based not on rigid entry criteria but on the "**uncertainty principle**". That is, if the doctor considers, for any reason, that there is a **definite** indication for, or a **definite** contraindication against, donepezil then the patient is not eligible for **AD2000**. If, on the other hand, the doctor is **substantially uncertain** whether or not a particular patient would derive worthwhile benefit from donepezil then that patient is **eligible to be randomised between donepezil and placebo**. In these circumstances randomisation is both scientifically and ethically preferable to the uninformative alternative of not randomising and treating patients in an *ad hoc* way outside of a study. (Those patients in whom donepezil is considered to be definitely indicated can be offered donepezil off study but do not contribute any useful information on the real value of donepezil.) Eligibility based on uncertainty has been used in many previous trials (e.g. the "ISIS" trials, the MRC International Stroke Trial, and the MRC carotid endarterectomy study⁵⁵) and has been shown to simplify trial procedures and to facilitate large-scale recruitment of an appropriately heterogeneous group of patients.

4. TRIAL PROCEDURES: RANDOMISATION

Simple eligibility: Alzheimer's disease, not in residential care, with a regular carer, and no "definite" contraindications to donepezil.

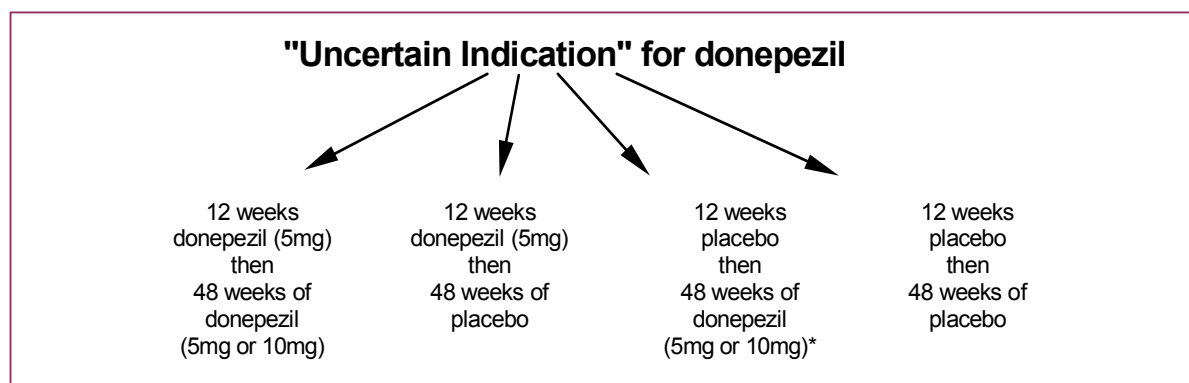
All patients are eligible if they are thought by the responsible physician to have a DSM IV diagnosis of Alzheimer's disease⁵⁶, with or without evidence of vascular dementia, to have no definite contraindications to donepezil, they are not in residential care, and they are not already taking donepezil or any other cholinergic enhancing agent. Definite contraindications to donepezil are not specified by the protocol but by the responsible physician. The only clear contraindication listed on the Aricept data sheet is hypersensitivity to donepezil or piperidine derivatives. Special precautions are advised for:

- anaesthesia
- cardiovascular conditions – particularly sick sinus syndrome or other supraventricular cardiac conduction conditions
- gastrointestinal conditions – history of high risk of peptic ulceration
- genitourinary – bladder outflow obstruction
- neurological conditions – seizures
- pulmonary conditions – asthma or obstructive pulmonary disease

Other conditions associated with only a small likelihood of worthwhile benefit may also be seen as contraindications, such as:

- severe dementia unlikely to respond to donepezil
- some **major** life threatening disease other than Alzheimer's disease
- low probability of treatment compliance (e.g. no regular carer).

The decision on whether there is a really **definite** indication for, or a **definite** contraindication against, donepezil, or whether the indication is still somewhat **uncertain**, and the criteria on which it is based, are left entirely to the responsible physician. Even within one participating hospital different doctors may decide differently as to the categories of patient for whom the indication for donepezil is **uncertain** (randomising such patients between donepezil and placebo).



* Patients allocated 10mg after an initial 12 weeks of placebo will receive the first 12 weeks of active treatment at 5mg/day before dose escalation.

Patient and carer information leaflet

The conduct of the study will be in accordance with the MRC policy on ethical considerations. The patient's and carer's consent (according to usual local practice) to participate in the trial must be obtained before randomisation and after a full explanation has been given of the treatment options, and the manner of treatment allocation. Patient information sheets are provided in the **AD2000** trial folder (Appendix A) so that patients and their carers can find out more about **AD2000** before deciding whether or not to participate. The patient's GP should be notified that they are taking part in **AD2000**, and a specimen "Letter to GP" is provided for this purpose also (Appendix F).

Randomisation: AD2000 notepads may be used

Patients are entered and randomised into the trial by one telephone call, or by one fax, to the randomisation service (telephone number **0800 371 969** or **0800 731 7625**, toll-free in the UK, or **+44 (0) 121 414 3586** from elsewhere; fax: **0800 731 7625**). The person randomising will need to answer

all of the telephone questions, and completing the **AD2000** randomisation notepad (Appendix B) before calling may help in preparing for them. Alternatively, randomisations can be faxed to the **AD2000** study office who will call back with a treatment allocation within one working day.

5. TRIAL PROCEDURES: TREATMENT

Donepezil or placebo from AD2000 treatment box

After all the necessary details have been provided, a unique patient treatment box number will be specified at the end of the telephone call. The treatment box number should be entered on the **AD2000** prescription form which is provided in the study folder. The patient and/or carer should be escorted to the hospital pharmacy to collect the first 12-week treatment pack from the **AD2000** treatment box with this number ^a. (If allocated aspirin, this should also be prescribed and obtained from the pharmacy at the same time – see below). The treatment box contains an envelope with pre-printed, numbered stickers which should be collected by the accompanying person as well as an unnumbered stamped addressed **AD2000** box which contains the materials needed to take the blood sample for the genetics study. Instructions for the trial treatments are available on a label which can be stuck in the patient's clinical notes. The psychiatrist or nurse should use the materials in the blood sample box to obtain the blood sample for molecular genetic analysis, label it with the patient's treatment box number using one of the stickers provided in the **AD2000** treatment box and post the sample on the same day. The treatment box labels with the patient's unique treatment box number should also be used to identify the patient assessments. The treatments should start as soon as possible, ideally within a week of randomisation, and should be continued for sixty weeks (five 12-week treatment packs) unless a definite contra-indication is thought to have developed. Transition to residential care is not necessarily a reason for discontinuation. If trial treatments are discontinued, the **AD2000** office should be notified of the reason (toxicity, lack of perceived effectiveness, or other), and the remaining drugs returned to the **AD2000** freepost address.

On completion of treatment there will be a 6-week period without any treatment after which the patient will be re-assessed. Further treatment is at the discretion of the responsible clinician. On present evidence, no recommendation can be made about treatment beyond 60 weeks but the Data Monitoring Committee (see p.19) will scrutinise the accumulating data from AD2000 and, if clear evidence for or against continued treatment emerges, will notify the Steering Committee who will then make appropriate recommendations.

Open label aspirin

Patients who are not already taking regular aspirin - and with no clear indication for, or clear indication against, aspirin - will be sub-randomised to receive aspirin (enteric-coated 75 mg/day) or to avoid aspirin - using paracetamol as necessary as an analgesic. If allocated aspirin, twelve weeks aspirin should be prescribed and obtained from the pharmacy when collecting the AD2000 treatment box. Treatment should continue indefinitely unless a clear contra-indication arises or the Data Monitoring Committee advises otherwise.

Side-effects of donepezil

Donepezil is generally well tolerated with few significant side-effects which usually resolve without the need to discontinue treatment. Diarrhoea, muscle cramps and nausea are most common and are expected to occur in about 10% of patients. Vomiting is expected in about 5% of patients, as is insomnia. Little difference in toxicity is anticipated between the 10mg and 5mg donepezil groups because the drugs will be packed in such a way that all patients allocated 10mg will receive donepezil at 5mg/day for 12 weeks before their dose is escalated to 10mg/day. Side-effects should be treated according to local policy. Serial liver function tests are not considered necessary. If serious toxicity is present, the **AD2000** clinical co-ordinators may be contacted (call **0121-414 7627/7560** during office hours) for advice.

^a The pharmacy at each participating centre will be supplied with an AD2000 trial case with eight numbered individual patient treatment boxes. Each box will contain five 12-week treatment packs of 3 x 28 blister-packed capsules containing either 5 or 10mg of donepezil or placebo (a total of 60 weeks treatment at one capsule a day).

Unblinding should not normally be necessary as **serious** side-effects should be dealt with on the assumption that the patient is on active donepezil treatment. If considered **definitely** necessary for patient management the randomisation service can be telephoned to unblind trial treatments (0800 371 969 or 0800 731 7625). The **medical** reason for unblinding must be provided.

Serious and unexpected adverse events

Donepezil is a relatively new drug, so **serious unexpected** adverse experiences ^b **believed to be due** to the **AD2000** treatment should be reported as soon as possible by telephoning the randomisation service. Following the telephone report, a Serious Adverse Event Form (see Appendix G) should be completed and sent to the **AD2000** Study Office within two weeks. Events that might reasonably be expected in elderly patients with Alzheimer's disease do not need to be reported in this way.

Follow-up assessments

Each time a patient is issued one of the five 12-week treatment boxes an appointment should be made for a return follow-up assessment of the patient and carer (Appendix D) **two weeks before scheduled completion of the treatment**. (This is to ensure that the patient is still taking trial treatment at the assessment even if their appointment has to be put back a week for any reason). After completion of the treatment the patient is re-assessed after a 6-week treatment-free period. Appointment cards are included in the AD2000 study folder to facilitate this. It is important for the analysis of the study that the reasons are ascertained for patients who default from follow-up. If possible, the principal carer should be asked by telephone, to complete the Carer's and Patient's details form (Appendix D2) and the Bristol Activities of Daily Living (Appendix D3). The minimum information that needs to be ascertained is whether or not the patient is in residential care and the patient's current functioning level – i.e. have they lost 2 of 4 basic and/or 6 of 11 instrumental activities of living (see p.7).

Other management at discretion of local doctors

Apart from giving out the trial treatments, and undertaking the follow-up assessments, all other aspects of patient management are entirely at the discretion of the local doctors. Patients are managed in whatever way appears best for them, with no special treatments, no special investigations, and no extra follow-up.

Long-term Follow-up

Follow-up of patients who have completed trial treatment will be obtained through an annual questionnaire to carers for at least two further years. The principal caregiver will be asked to complete the Carer's and Patient's details questionnaire (Appendix D2) and the Bristol ADL (Appendix D3) to provide brief details of the patients current status. Long-term follow-up of mortality will be obtained through central government records.

6. SIZE OF DIFFERENCE TO BE MEASURABLE

Projected accrual

With widespread collaboration, it is estimated that some 3000 patients (less than 1% of an estimated total of more than 400,000 patients with Alzheimer's diseases in the UK), from 50 participating centres, could be randomised in **AD2000** over 1 to 2 years. The 1500 allocated donepezil from week 13 onwards will be sub-randomised, at entry, between 5mg and 10mg of donepezil. It is estimated that about half of the patients (1500) will not already be taking aspirin, or have a potential positive indication for, or definite contra-indication against, aspirin. These patients will be sub-randomised between daily aspirin and avoiding aspirin.

All analyses will be by "intention-to treat" using standard logrank and chi-square techniques. Based on

^b For the purposes of this study, "**serious**" adverse events are those which are fatal, life-threatening, disabling or require hospitalisation. "**Unexpected**" adverse experiences are defined as those that would not be expected among elderly patients given donepezil (which has certain expected side-effects such as nausea, diarrhoea, etc.) for Alzheimer's disease (which has expected symptoms). It is not required to report in this way side-effects or events that might reasonably be expected following donepezil treatment of dementia, such as disease progression or death from dementia.

the US trial of vitamin E and selegiline⁴⁵, the severe disability rate at two years for moderate Alzheimer's disease is estimated to be around 25%. For mild Alzheimer's disease, it is also estimated that about 25% will lose six out of eleven instrumental activities of daily living. 3,000 patients would allow detection of a 20% proportional reduction in these rates, which would be medically worthwhile, i.e. from 25% to 20%, at $p < 0.05$, with 90% power. The subsidiary analysis of short-term (12 week) response will have even greater statistical power as the 1500 patients allocated placebo for the first 12 weeks, and then allocated to either donepezil or placebo for the remainder of the trial will also contribute to the 12 week comparison. Thus, with 4,500 donepezil-naive patients randomised between 12 weeks of donepezil and placebo (and another 1500 who had previously received 12 weeks of donepezil), there would also be a more than an 90% probability of detecting a 5% absolute difference in, for example, psychiatric disorders in carers at the 12 weekly assessments (e.g. 30% vs 35%) between donepezil (any) and placebo, at $p < 0.05$.

With 1500 randomised between 10mg and 5mg of donepezil, and 1500 between aspirin and no aspirin, there will be an 80% probability of identifying a 25% proportional reduction in progress of disability (25% vs 19%) from using 10mg rather than 5mg of donepezil or from aspirin. Quantitative treatment interactions (e.g. greater treatment effect in moderate than mild dementia) will not materially affect these calculations. A prior hypothesis is that alleviating the burden on carers will delay transition to formal domiciliary or residential care and so this analysis will be undertaken using a one-tailed test, if highly significant reductions in carer burden are seen with donepezil.

If a clear benefit of donepezil emerges on the primary endpoints then subgroup comparisons will generally be undertaken using cognitive function as a surrogate measure – which will substantially increase the statistical sensitivity of these analyses. The following subgroup analyses will be explored – appropriately cautiously:

Pre-treatment variables:

- (a) Diagnostic group: DSM IV Alzheimer's disease, mixed DSM IV Alzheimer's disease and vascular dementia;
- (b) Presence or absence of Parkinsonian symptoms;
- (c) Presence or absence of psychotic symptoms;
- (d) Severity of dementia as assessed by MMSE: mild (19-26), moderate(10-18), severe (<10);
- (e) Age at randomisation: <60, 60-69, 70-79, 80+;
- (f) Apolipoprotein E genotype: $\epsilon 4$ polymorphism present or absent;

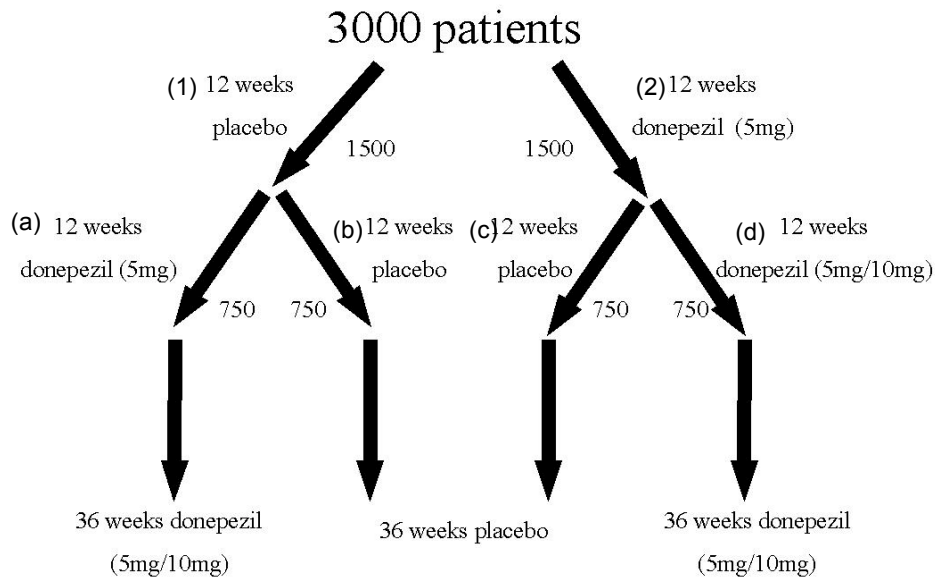
Post-treatment variables:

- (g) Treatment period: 1-12 weeks, 13-24, 25-36, 37-48, 49-60; and 61+;
- (h) Response at 12-week assessment as measured by change in MMSE over baseline: good response (≥ 4 points improvement), moderate response (2-3), no change (-1 to +1), progression (< -1);

Full efficiency: the AD2000 factorial design allows separate assessment of short (12 week) and long (48-week) donepezil treatment without any material effect on study size requirements

Four different combinations of donepezil and placebo are described below, each with 750 patients (among whom 1,500 patients will be sub-randomised between 5mg and 10mg of donepezil, and for aspirin or not). This factorial design makes best use of available patients because it allows each question to be answered about as reliably as it would have been if only one question were being asked⁵⁷.

Trial Schema



Notes on the analyses

- Assessment of the effect of 12 weeks of donepezil involves a combined analysis of the comparisons between groups (1) and (2), (a) and (b), and (c) and (d).
- Sub-comparisons between the size of treatment effect for (1) vs (2) and (a) vs (b) will assess whether treatment delay is deleterious, and comparisons between the treatment effects for (1) vs (2) and (c) vs (d) whether prior donepezil treatment affects subsequent response.
- Assessment of the effects of 48 weeks of donepezil involves a combined analysis of the comparisons of groups (a) vs (b) and (d) vs (c).
- Again, comparison of the effect of 48 weeks of donepezil with 48 weeks of placebo does not involve any implicit assumptions about prior use of donepezil, for the comparison will be “retrospectively” stratified for previous exposure to donepezil.

Data monitoring committee: determining when clear answers have emerged

If donepezil really does produce substantial short-term and/or longer-term clinical and social benefits then this may become apparent before the target recruitment has been reached. Alternatively, other drugs might emerge that are definitely more effective than donepezil.

To protect against this, during the period of intake of the study, interim analyses of major endpoints will be supplied, in strict confidence, to an independent data monitoring committee (DMC) along with updates on results of other related studies, and any other analyses that the committee may request. The DMC will advise the chair of the trial’s steering committee if, in their view, the randomised comparisons in AD2000 have provided both (a) “proof beyond reasonable doubt”^c that for all, or for some, types of patient one particular treatment is definitely indicated or definitely contraindicated in terms of a net

^c Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.

difference in the primary endpoints, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. The steering committee can then decide whether to modify intake to the study. Unless this happens, however, the steering committee, the collaborators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain ignorant of the interim results.

If the clinical coordinators are unable to resolve any concern satisfactorily, collaborators, and all others associated with the study, may write through the **AD2000** trial office to the chairman of the data monitoring committee, drawing attention to any worries they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

7. ORGANISATION

To ensure the smooth running of **AD2000** and to minimise the overall procedural workload, it is proposed that each participating centre should designate individuals who would be chiefly responsible for local coordination of clinical, pharmaceutical and administrative aspects of **AD2000**:

Local Co-ordinator at each centre

Each Centre should nominate one person to act as the Local Coordinator. Their responsibilities will include:

Applying for Local Research Ethics Committee (LREC) approval for AD2000 on behalf of their Centre. The **AD2000** study has already obtained Multi-centre Research Ethics Committee approval which should greatly simplify obtaining LREC approval. The AD2000 Study Office will help the local coordinator by supplying an LREC submission pack (or by completing the form on behalf of the centre), by providing lists of local doctors who have expressed interest in **AD2000**, and by helping resolve any local problems that may be encountered in trial participation. As soon as LREC approval has been obtained, the **AD2000** Study Office will send an AD2000 folder containing all trial materials to the local co-ordinator, and an AD2000 treatment case to the nominated pharmacy contact (see below). Randomisation can then begin.

To ensure that all medical and nursing staff involved in the care of Alzheimer's disease are reasonably well informed about the study. This involves distributing AD2000 protocols and patient information sheets to all relevant staff, displaying the wall-chart where it is likely to be read, and distributing the plastic protocol summaries (which can be carried in the pockets of the medical and nursing staff) and the regular newsletters. A set of regularly updated AD2000 slides will be provided for each hospital so that they can be shown from time to time, especially to new staff.

Chief Pharmacy contact at each centre

Once Ethics Committee approval has been obtained, the **AD2000** study office will despatch a case containing eight individual patient treatment boxes to each participating Centre. The Local Coordinator should give the trial office the name of the Pharmacy (or other) contact to whom the **AD2000** treatment case, information about the study, and dispensing instructions should be sent. The Pharmacy contact will then receive further supplies automatically, as required, and will be sent information on any future changes in dispensing instructions, etc, as well as newsletters and invitations to **AD2000** meetings.

Chief Nursing Co-ordinator at each centre

It is suggested that each participating centre should designate one nurse as Local Nursing Coordinator. This person would be responsible for ensuring that all eligible patients are considered for **AD2000**, that patients and carers are provided with **AD2000** information sheets (Appendix A), and have an opportunity to discuss the study if required, for administering the MMSE (Appendix C), carer questionnaire (Appendix D), and shortened NPI (Appendix E) at the routine 12-weekly follow-up assessments, and for ensuring that **AD2000** trial treatments are obtained from the Pharmacy and handed out as scheduled upon receipt of the fully completed patient assessments (unless some contraindication develops). Again, this person would be sent updates and newsletters, and would be invited to **AD2000** training and progress meetings.

Central co-ordination: supply of all trial materials, randomisation service, and data collection and analysis

The **AD2000** Study Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for

providing the specially packed trial cases containing treatment packs, the trial folders containing printed materials, and the **AD2000** slides. These will be supplied to each collaborating centre, after relevant ethics committee approval has been obtained. Patient entry in a centre can start as soon as the first drug supplies are received. Further supplies will be delivered **automatically** by the coordinating centre. Additional supplies of any printed material can be obtained on request. The **AD2000** trial office also provides the central randomisation (and unblinding) service and is responsible for collection of data (including reports of serious adverse events thought to be due to trial treatment) and for data analyses.

Finance

The **AD2000** trial organisation is funded by a grant from the NHS Executive R&D (West Midlands) to the University of Birmingham Clinical Trials Unit. Donepezil is manufactured by Eisai Limited and is marketed by Pfizer Limited. However, the **AD2000** study is not sponsored by either Eisai Limited or Pfizer Limited. Neither company contributed to the study design or protocol, and neither has been or will be involved in the management or reporting of the study. Eisai Limited's and Pfizer Limited's activity in relation to the study is limited to the provision of **AD2000** study drug and placebo to the University of Birmingham Clinical Trials Unit on a commercial basis. These drugs are being paid for by the West Midlands Health Authorities. The general structure of the study was, however, designed independently of NHS purchasers or any pharmaceutical companies, who have no representative in its organisation and who will, like the steering committee, remain blind to the results as they accumulate. This arrangement is intended to ensure that no suggestions of lack of objectivity of the findings can be justified.

Cost implications

AD2000 has been designed to minimise extra costs for participating hospitals. The drugs are supplied free-of-charge within the West Midlands. Centres outside the West Midlands are also encouraged to participate but local arrangements for financing trial drugs (at £700/patient) will need to be in place before patient entry can commence. The **AD2000** Study Office can help with this. **AD2000** thus involves less 'treatment costs' than would use of donepezil outside the study. Other costs are minimal. Donepezil is a simple out-patient treatment, and the patient assessments and follow-up schedule in **AD2000** are only marginally more than those which would be required as standard patient care if these patients were treated with donepezil in an uninformative *ad hoc* way outside the study. To cover the extra clinics, nursing and pharmacy time involved a per patient payment of £90 will be made to offset these 'excess treatment costs'. These payments will be made through the **AD2000** Study Office. Centres may wish to join together in a consortium to employ a peripatetic research nurse to run the follow-up clinics with this money. Again, please contact the **AD2000** study office who may be able to help organise this.

Indemnity

Aricept is licensed for symptomatic treatment of mild or moderate dementia in Alzheimer's disease. There are no special arrangements for compensation for non-negligent harm suffered by patients as a result of participating in the study. **AD2000** is not an industry-sponsored trial and so ABPI guidelines on indemnity do not apply. The manufacturers of donepezil have not been involved in any way in the design or conduct of the trial. **AD2000** is funded chiefly by the NHS Executive R&D (West Midlands) on behalf of Health Authorities in the West Midlands. The normal NHS indemnity liability arrangements for clinician – initiated research⁵⁸ will operate in **AD2000**. However, it should be stressed that in terms of negligent liability, NHS Trust and non-Trust hospitals have a duty of care to a patient being treated within their hospital, whether or not that patient is participating in a clinical trial.

Publication and ancillary studies

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators **prior** to publication. The success of **AD2000** depends entirely on the wholehearted collaboration of a large number of doctors, nurses and others. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study.

It is requested that any proposals for formal additional studies of the effects of the trial treatments on some **AD2000** patients (e.g. special investigations in selected hospitals) be referred to the steering committee for consideration. In general, it would be preferable for the trial to be kept as simple as possible, with very few add-on studies.

APPENDIX H: REFERENCES

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