NETSCC, HTA

2nd February 2011

A large randomised assessment of the relative cost-effectiveness of different classes of drugs for Parkinson's disease

PROTOCOL

Parkinson's disease (PD) is one of the commonest causes of disability in older people with at least 8,000 new cases diagnosed each year in the UK alone. Levodopa (LD) controls symptoms for most patients but long-term use is associated with motor complications. A number of other drugs have been used, either alone or with reduced doses of LD, in an attempt to delay the onset of motor complications, or to control complications in later disease once they have developed. These agents have primarily been from three classes of drug: dopamine agonists (DA), monoamine oxidase type B inhibitors (MAOBI) and catechol-O-methyltransferase inhibitors (COMTI).

All of these drugs are beneficial, but there is uncertainty about their relative effectiveness. This is because previous comparative studies included too few patients, most had inadequately short follow-up, and the overall impact of the drugs on the patient's quality of life was not properly assessed. For example, DAs delay the onset of motor complications compared to LD, but this needs to be balanced against poorer control of the symptoms of PD, and worse side-effects - including nausea, hallucinations, sleep disturbance and oedema - which may be more important for patients and carers than motor complications. There are also uncertainties about the role of the potentially neuroprotective MAOBI, selegiline, partly because the UK PDRG trial closed early when an increase in mortality was seen with selegiline compared to LD. However, this has not been confirmed in other studies. Similarly, the COMTI, entacapone, is becoming widely used in later disease, but its efficacy compared to alternative drugs is uncertain. The new DAs and COMTIs are considerably more expensive than either LD or selegiline, and more reliable evidence is needed on the balance of benefits and risks of these drugs to establish their relative cost-effectiveness.

PD MED is a large, simple, "real-life" trial that aims to determine much more reliably which class of drug provides the most effective control, with the fewest side-effects, for both early and later PD. Patients with early PD are randomised between DA, MAOBI and LD alone, with the option to omit either the MAOBI or LD alone arm. Those whose disease is no longer controlled by their first class of drug, after dose titration and/or addition of LD, are randomised between COMTI, MAOBI and DA, with the option to omit either the MAOBI or the DA arm. The main outcome measure is the patient-rated PDQ-39 quality of life scale, which assesses all aspects of the patient's life, and is sensitive to changes considered important to patients but not identified by clinical rating scales.

*optional arm

In order to recruit the large number of patients needed to provide reliable answers, and to maximise the clinical relevance of the findings, the trial is designed to fit in with routine practice as far as possible and to impose minimal additional workload: clinicians can use the specific drug within each class that they prefer, treatments are prescribed in the usual way, and extra clinic-based tests and evaluations have been kept to a minimum (the majority of assessments are by postal questionnaires to patients and carers). Because the success of the trial depends entirely on the whole-hearted collaboration of a large number of doctors, nurses and others, publication of the main results will be in the name of the collaborative group and not those of the central organisers.

PD MED is funded by the NHS Health Technology Assessment programme and is supported by the European Parkinson's Disease Association, the Parkinson's Disease Society and the Parkinson's Disease Nurse Specialist Association

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“There are nearly no data for comparisons between interventions. If choices among equivalent therapeutic options will always remain a matter of clinical expertise and individual preferences, a lot remains to be done to identify which options are equivalent. Similarly, there is a lack of data to assess the potential interest of simultaneous or successive combinations of different interventions. There are insufficient data on long-term outcomes and mortality. We hope that, by pointing out these insufficiencies, we will encourage the scientific community to do the appropriate investigations to correct such lacunas.”

Olivier Rascol, Christopher Goetz, William Koller, Werner Poewe, Cristina Sampaio
Treatment interventions for Parkinson's disease: an evidence based assessment.
Lancet 2002; **359**: 1589-98

“Substantial uncertainties about fundamental aspects of treating Parkinson's disease remain, and after decades of research into both early and later Parkinson's disease we still have little evidence on which to base decisions between different classes of drug.”

Keith Wheatley, Rebecca L Stowe, Carl E Clarke, Robert K Hills,
Adrian C Williams, Richard Gray
Evaluating drug treatments for Parkinson's disease: how good are the trials?
BMJ 2002; **324**:1508-11

“Most trials of drug treatment for Parkinson’s disease have crucial methodological faults - and provide little reliable evidence on differences between classes of drugs.”

BMJ Commentary. BMJ 2002:**324**:1508

“**More reliable evidence is needed on the balance of benefits and risks of the new DAs to establish their cost-effectiveness. Future trials should include global measures of the patient's quality of life as primary outcome measures.”**

N.J. Ives, R.L. Stowe, L. Shah, R.J. Hawker, C.E. Clarke, R.G. Gray, K. Wheatley
Meta-analysis of 5038 patients in 28 randomised trials comparing dopamine agonists with levodopa
6th International Conference AD/PD 2003 Seville, Spain May 8-12, 2003. Abstract no. 469

“……the long-term benefits of initial dopamine agonist therapy remain unproven. A very large trial currently under way in the United Kingdom (PD MED) is randomizing hundreds of subjects to initial treatment with LD/DI preparations, dopamine agonists, or selegiline. Five-year follow-up is projected. Outcomes evaluated will include quality of life, cost-effectiveness, and incidence of motor complications. Widespread changes in clinical practice should await the accumulation of more trial data.”

R.L.Albin, K. A. Frey
Initial agonist treatment of Parkinson disease. A critique
Neurology, 2003; **60(3)**: 390-394

1. BACKGROUND

1.1. Parkinson's Disease

Parkinson's disease (PD) is a progressive neurological disorder caused by the loss of pigmented dopaminergic neurones in the brain and the consequent depletion of the neurotransmitter dopamine. This leads to increasing disability due to motor complications, including tremor, rigidity, slowness, and postural disturbance. PD is one of the commonest causes of disability in older people. It is estimated that at least 8,000 new cases of PD are diagnosed in the U.K. each year. Average life expectancy is about 15 years, leading to a prevalence of over 100,000 cases and incidence increases rapidly with age, 95% of patients are aged over 40 years at diagnosis, with most patients developing the initial symptoms of PD between 50 and 70 years of age. There is currently no curative therapy for PD, so treatment is directed towards the alleviation of symptoms.[1]

1.2. Treatment of early PD

Levodopa (LD) provides good symptomatic relief for most patients with PD and may improve their survival.[2, 3] However, after a few years of treatment, motor complications ("wearing-off", "on-off" fluctuations and dyskinesia) often develop. It is unclear to what extent these complications are due to disease progression or to cumulative LD effects. Dopamine agonists (DAs) and monoamine oxidase type B inhibitors (MAOBIs) have been used, either alone or with reduced doses of LD, in an attempt to delay the onset of motor fluctuations. A systematic review of the existing randomised evidence confirms the increased risk of motor complications with LD, but also indicates that disease control is not as good and other side-effects are increased with DAs. The available evidence from randomised trials assessing the various therapeutic options in PD, published prior to January 2003, is shown below (see Table 1). As outcome data are inconsistently reported, an informal non-quantitative scoring system is used to indicate outcome.

Table 1 : Summary of results of randomised trials of dopamine agonists and dopamine degradation inhibitors (MAOBIs and COMTIs) in early Parkinson's disease

Comparison	No. of trials (patients)	Mean follow-up (years)	Clinical disability scales	Motor Complications	Other side effects	LD Dose Reductions
Levodopa v placebo[3]	1 (361)	0.8	++	++	-	n/a
DA v placebo (± LD)	11 (1308)	0.9	++	No data	- -	+
MAOBI v placebo (± LD)	13 (1485)	3.5	+	o	(-)	+
COMTI v placebo (± LD)	2 (381)	0.8	(+)	(+)	(-)	+
DA (± LD) v LD	21 (4393)	4.6	-	++	- -	+
MAOBI (± LD) v LD	2 (852)	7.2	o	(+)	o	No data
MAOBI v DA (± LD)	1 (335)	2.8	o	o	No data	(-)
Other[$]	7 (1091)	6.2				
TOTAL	**46 (8072)**	**3.7**				

(+) = possible benefit; + = small benefit; ++ = moderate benefit; o = no difference; (-) = possible adverse affect; - = small adverse affect; - - = moderate adverse effect (scores indicate benefit, or harm, from left hand comparator)

Patients in 5 trials with multiple comparisons count towards more than one comparison but just once to the total, which give the actual numbers of trials, patients randomised and follow-up lengths.

[$] Other early disease comparisons included DA v DA (±LD), DA (+MAOBI) v LD, DA (+MAOBI) v DA, DA (+MAOBI) v MAOBI (+LD).

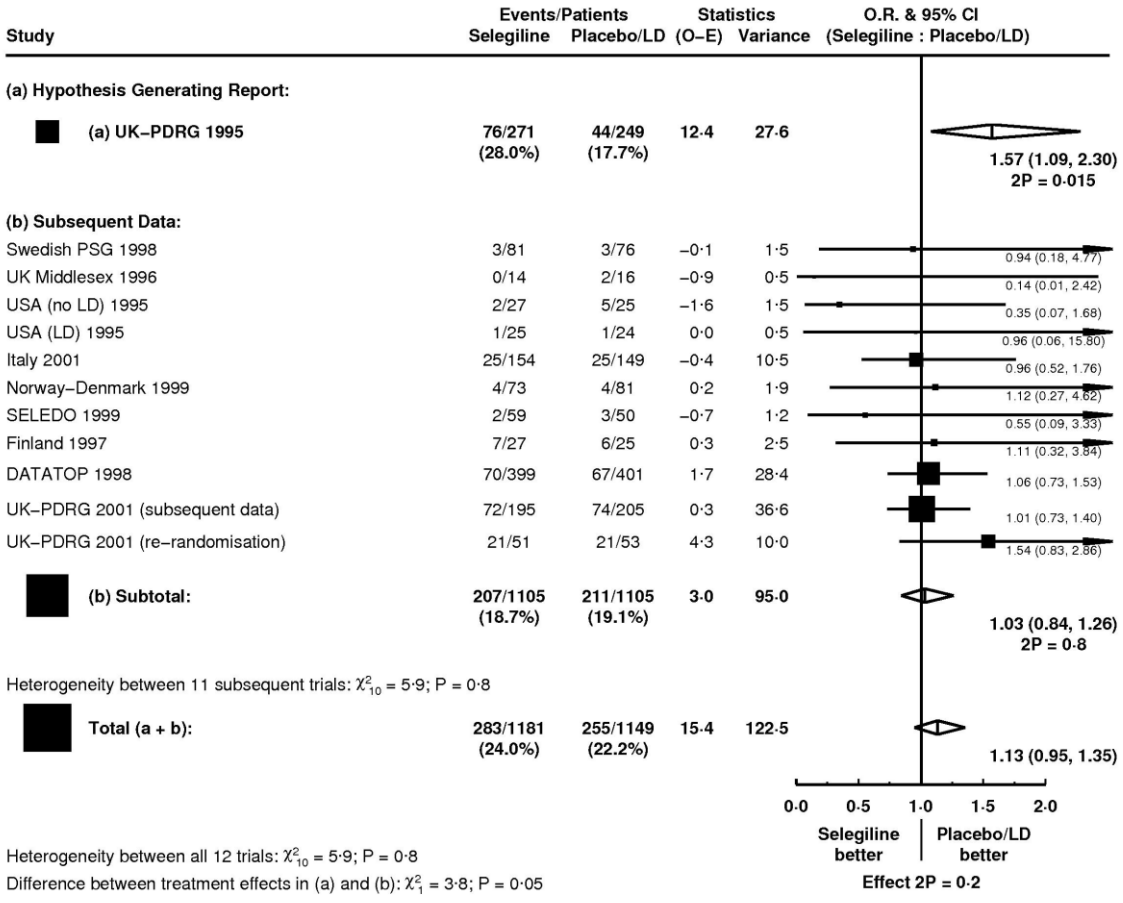
Abbreviations: LD = levodopa; DA = dopamine agonist; MAOBI = monoamine oxidase type B inhibitor; COMTI = catechol-O-methyltransferase inhibitor

For detailed information on trials included in the table, see references 3 & 8.

Dopamine agonists: Dopamine agonists (DAs) are widely used as add-on therapy in later disease, and are now being increasingly used in first-line treatment, particularly for younger patients. Trials comparing DA with placebo in early disease have generally reported improved outcome with DA, usually with respect to one of a number of clinician-scored impairment/disability scales, most commonly the Unified Parkinson's Disease Rating Scale (UPDRS). Trials comparing DA (with LD introduced as necessary) with LD alone have established benefits for DAs in terms of delaying the onset of motor complications, with reductions in dyskinesia and in the dose of LD required.[4-7] However, symptomatic control is inferior with DAs and some side-effects, including nausea, oedema, hallucinations, constipation, dizziness and sleep disturbance, are increased by DAs. As previous trials have failed to assess the overall impact of the drugs on the patients' quality of life, it is unclear whether DAs are superior to LD, from the patients' perspective. The newer DAs (pergolide, ropinirole, cabergoline and pramipexole) are considerably more expensive than LD, or the older DA, bromocriptine, and their relative cost-effectiveness needs to be more reliably assessed. Very few trials have directly compared one new DA with another and hence there is no reliable evidence on whether particular DAs are better than others.[8,9]

MAOB inhibitors: Inhibitors of dopamine degradation, such as the monoamine oxidase type B inhibitors (MAOBIs), are a second class of drugs that has been widely used as LD-sparing therapy in early PD, or as an add-on to LD in later PD. Trials of selegiline, the most frequently used MAOBI, versus control, with or without LD in both arms, in early PD have consistently shown improvements in the UPDRS and other disability scales with selegiline. These trials have also demonstrated that selegiline treated patients can be maintained on lower doses of LD, and provide some support for a neuroprotective effect of selegiline. However, the largest trial of selegiline plus LD versus LD alone was halted prematurely because of increased mortality in the selegiline arm compared to LD, raising concerns about its use. [10,11] Subsequent data, including later follow up from the initial adverse study, show no increase in deaths with selegiline[12-15] and a meta-analysis of all trials confirms this.[16] In total, 283 (24%) deaths have occurred among 1181 selegiline allocated patients and 255 (22%) among 1149 control patients, a non-significant difference (see below).

Meta–analysis of deaths in trials of selgiline



It seems highly likely, therefore, that the excess deaths with selegiline in the UK-PDRG trial, which was of only borderline statistical significance, was a chance finding. Nonetheless, this "scare" has had the effect of reducing the use of selegiline, an inexpensive drug which may be the most cost-effective drug available for treatment of early PD. This reassuring finding, plus the recent licensing of a new MAOBI, rasagiline, has revived interest in MAOBIs as an alternative LD-sparing therapy. There is, unfortunately, only one trial comparing MAOBIs with DAs in early PD and hence no good evidence on the relative effectiveness of MAOBIs compared to the more expensive DAs is available. A sub-lingual form of selegiline is also available but, again, this has not been properly evaluated in large randomised trials.

1.3. Treatment of later PD

Once dyskinesia, "wearing-off" and "on-off" fluctuations develop with LD monotherapy, it is unclear which drugs should be introduced. DAs and dopamine degradation inhibitors (DDIs), such as MAOBIs and the newer catechol-O-methyltransferase inhibitors (COMTIs), are commonly used. However, there is even greater uncertainty as to the relative value of these alternatives as even fewer patients with later PD have been entered into randomised comparative trials than with early disease. Most trials have compared LD plus another drug with LD alone with the largest body of evidence on the role of DAs. Almost all trials have been short-term with a mean duration of less than 6 months. Table 2 summarises the results in an informal non-quantitive fashion, as with Table 1.

Table 2 : Summary of results of randomised trials of dopamine agonists and dopamine degradation inhibitors (MAOBIs and COMTIs) in later Parkinson's disease

Comparison[#]	No. of trials (patients)	Mean follow-up (years)	Clinical disability scales	Other side effects	LD dose reductions
DA v placebo	23 (2231)	0.5	++	(-)	+
MAOBI v placebo	17 (498)	0.4	++	(-)	+
COMTI v placebo	16 (2166)	0.5	++	(-)	+
DA v DA	9 (1265)	0.5	N/A	N/A	N/A
COMTI v DA	3 (499)	0.2	0	0	0
TOTAL	68 (6472)	0.5			

See Table 1 footnote

Patients in one multiple comparison trial count towards more than one comparison but just once to the total, which give the actual numbers of trials, patients randomised and follow-up lengths.

[#]All trials in later PD are on a background of LD-based therapy.
Abbreviations: PD = Parkinson's disease; LD = levodopa; DA = dopamine agonist; MAOBI = monoamine oxidase type B inhibitor; COMTI = catechol-O-methyltransferase inhibitor

For detailed information on trials included in the table, see reference 8.

Dopamine agonists: Trials of DAs versus placebo in later PD have shown improvements in UPDRS scores with DAs and some reductions in “off” time. Patients receiving DA also required slightly lower doses of LD but side-effects appeared higher with DA. Few trials have directly compared one DA with another, although advantages for the newer DAs over bromocriptine have been suggested. For example, a Cochrane review of three trials of pergolide versus the older DA, bromocriptine, has reported a moderate benefit for pergolide on clinician-based rating scales.[17]There have been no trials comparing one new DA with another.

MAOB inhibitors: Eighteen trials of selegiline versus placebo in later PD have been undertaken, but the majority of these have been very small (with an average trial size of 30 patients) and have used cross-over designs aimed at evaluating short-term endpoints. The trials indicate a moderate benefit for selegiline with respect to "off" time and clinical disability scales. However, remarkably, only one trial[17] comparing MAOBI with either DA or COMTI has been undertaken in later PD. Comparative trials, including larger numbers, more clinically relevant endpoints, and longer term outcome assessments are needed.

COMT inhibitors: COMTI's are another class of dopamine degradation inhibitors. Trials of the COMTI's, tolcapone and entacapone, compared to placebo in later PD have shown improvements in "on" time, clinician-rated disability scales, and reduction in LD dose. Tolcapone was, however, withdrawn in Europe following three fatal cases of fulminant hepatitis in about 60,000 treated patients. Although tolcapone can cause liver toxicity, it is not certain that these fatalities were caused by tolcapone, and it remains possible that the potential benefits of tolcapone in later PD might out-weigh the risks. The newer COMTI, entacapone, has also shown some evidence of improvements in disability scales, and appears not to be hepatotoxic. Although tolcapone is now available again, it is recommended that COMTI treatment should commence with entacapone with tolcapone used only if an inadequate response to entacapone. Again, the efficacy of COMTIs compared to other classes of drug has not been properly assessed, with only three trials of tolcapone versus DAs having been identified, one trial of rasagiline versus entacapone, and no trials of COMTI versus the much less expensive DDI, selegiline.

1.4. The need for PD MED, a large 'real life' between-class comparison of PD therapies

Previous trials have, on the whole, been too small to evaluate reliably moderate differences between different classes of drug: even the largest trial accrued only 800 patients, and most recruited less than 50.8 Furthermore, the majority of trials have concentrated on short-term efficacy (many trials have used cross-over designs) and used physician-rated disability assessments as sole outcome measures. It is essential, in a slowly progressive disease such as PD, to evaluate the long-term effectiveness of treatment, based on clinically and socially important outcomes, and to assess the patients' perception of benefit as well as that of clinicians. Cochrane reviews are addressing a number of comparisons in PD treatment, but these are limited by serious methodological problems with some of the contributing trials (e.g. "major methodological problems preclude a conclusion on the efficacy of bromocriptine ",[18] "studies can be criticised for inadequate data on concealment of allocation, variable reporting of data on a per protocol or intention-to-treat basis and their short duration"[19]).

There is, therefore, an urgent need for much more reliable evidence on the balance of risks and benefits of LD-sparing therapy compared to LD alone in early disease, and on whether LD-sparing therapy with a DA or an MAOBI is preferable. The PD MED trial addresses this fundamental question, comparing DA versus MAOBI versus LD alone (with LD being added into the first two arms as necessary). Similarly, few data are available on the comparative efficacy of COMTIs, MAOBIs and DAs in later PD, and this question is also addressed in PD MED by a randomisation between DDI and DA, with a sub-randomisation between types of DDI (i.e. COMTI versus MAOBI), which will provide important new information on the relative efficacy of these different classes of drug.

PD MED does not directly compare different agents within particular classes of drug as this would require an impracticably large sample size. For example, there are five different DAs currently available and no good evidence that any particular DA is better than any other in either early or later disease. A randomisation between all five would require a very large sample size to allow for multiple comparisons and the consequent risk of false positive results. Choosing just two DAs (or three, at most) to compare would require an arbitrary choice and would decrease the flexibility of the trial should new evidence emerge during its course to suggest that any one particular DA may be of greater or lesser benefit. Inflexibility in choice of DA could also limit recruitment. Instead, there-fore, the choice of which DA to use in PD MED is left to the individual clinician. The DA will need to be specified at the time of randomisation, which will allow indirect comparisons of the efficacy of the various DAs, although such comparisons are statistically weak and will be used only in an exploratory hypothesis-generating sense.

As with DAs, the choice of MAOBI will be left to the individual clinician. Selegiline has been the most widely used and is also available in a sub-lingual formulation and a new MAOBI, rasagiline, was licensed in May 2005. Any of these may be selected, and the analyses will again be stratified by the MAOBI chosen, allowing indirect comparisons. Similarly, either entacapone or tolcapone (if inadequate response to entacapone) may be used as the COMTI. The withdrawal of licensing approval for tolcapone re-inforces the advisability of this pragmatic approach of allowing clinicians freedom of choice within a particular class of drug.

Thus, the first priority in PD MED is to answer reliably the fundamental qualitative question of which class of agents provides the most effective control of symptoms with the fewest side-effects. The quantitative questions of whether particular drugs within a class are more effective than others, or whether combinations of different classes of drugs are more effective than one class alone, will be questions for future trials.

2. TRIAL DESIGN

2.1. Separate randomisations in early and later disease

PD MED is a large, simple, "real-life", randomised assessment of the relative cost-effectiveness of different classes of drugs for both early and later PD.

The four fundamental questions being addressed by two semi-factorial randomisations in this trial are:

1. Does early treatment with levodopa-sparing therapy (either a DA or a MAOBI) delay deterioration in quality of life compared to LD alone?

2. Which class of LD-sparing treatment is preferable (DA or MAOBI)?

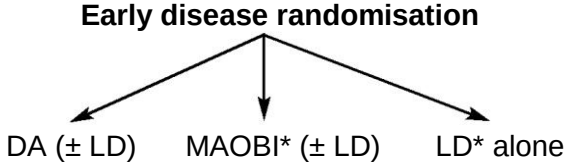
3. For patients with motor complications uncontrolled by LD alone, should DDIs or DAs be added to LD?

4. If so, which class of DDI (COMTI or MAOBI) is preferable?

2.2. Early PD randomisation

Patients recently diagnosed with PD (by UK Brain Bank diagnostic criteria Appendix A) are eligible for the early PD randomisation if:

1. They are previously untreated for PD and therapeutic intervention is considered appropriate. Patients not thought to require dopaminergic treatment at diagnosis are eligible once it is considered that such treatment becomes necessary.
or
2. They have previously been treated with dopaminergic medication, but for less than 6 months, and there is now uncertainty as to which class of drug to use. This randomisation may entail stopping, or modifying the previous therapy. This will be left to the discretion of the investigator.

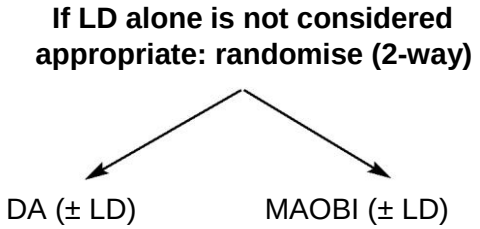


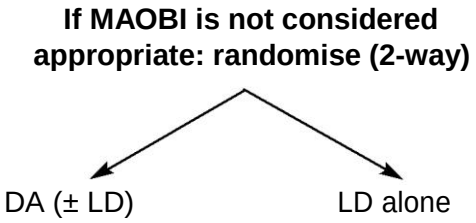
*optional arm

Question 1 will be addressed by comparison of arms 1 & 2 (DA or MAOBI) with arm 3 (LD alone).

Question 2 will be addressed by comparison of arm 1 (DA) with arm 2 (MAOBI).

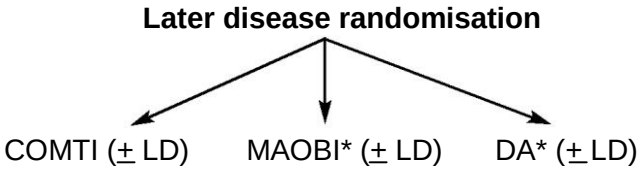
If treatment with either MAOBI or LD alone is considered to be **definitely** inappropriate for a particular patient, then this arm can be omitted. For example, some clinicians may consider that for particular types of patients (e.g. younger ones) LD alone is not appropriate and, in this circumstance, a two-way randomisation between DA and MAOBI may be performed. Similarly, if a clinician considers that a MAOBI is not appropriate, a patient may be randomised two-ways between DA and LD alone. Definite indications for, or definite contraindications against, any of the therapies in the trial are not specified by the protocol, but by the responsible clinician (see Section 3.1).





2.3. Later PD randomisation

Patients who develop motor complications that are uncontrolled by LD (alone or in combination with either DA or MAOBI), and hence require the addition of another class of drug are eligible for the later disease randomisation.

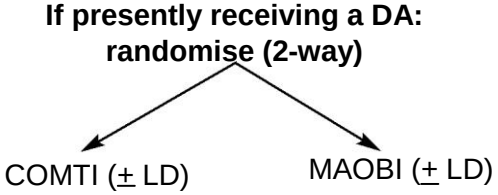


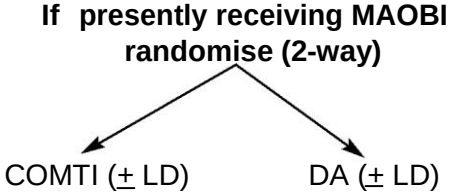
*optional arm

Question 3 will be addressed by comparison of arms 1 and 2 (COMTI or MAOBI) with arm 3 (DA).

Question 4 will be addressed by comparison of arm 1 (COMTI) and arm 2 (MAOBI).

Patients who were already receiving a DA when uncontrolled motor complications arose are not eligible for the DA arm but can be randomised between COMTI and MAOBI. Patients who were receiving a MAOBI when uncontrolled motor complications arose, or for whom the clinician considers that MAOBI treatment is definitely contraindicated, are not eligible for the MAOBI arm but can be randomised between COMTI and DA.





N.B. Patients who have been entered into the early disease randomisation should be re-randomised into the later disease randomisation if motor complications develop that cannot be controlled by drug dose titration and/or addition of LD if on DA/MAOBI.

3. LARGE, SIMPLE TRIAL: MINIMAL EXTRA WORKLOAD

The differences between active agents are likely to be smaller than those between any one agent and a placebo control. Thus, larger numbers of patients will be required for the reliable detection, or reliable refutation, of any worthwhile differences between different classes of drugs. To make widespread participation from a large number of centres practicable, the PD MED trial procedures are 'streamlined', with minimal extra workload placed on participating clinicians, beyond that required to treat their patients. This is achieved by simple entry procedures (a single phone/fax call to the randomisation office), the use of standard, open-label treatment regimens, follow-up as in routine practice (with no additional hospital visits or tests to be performed above those done as part of standard care), minimising documentation, and largely patient-based evaluation of outcome (through postal questionnaires). 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.

3.1. Simple eligibility and randomisation based on "uncertainty"

There is disagreement on the extent to which the development of motor fluctuations and dyskinesia after long-term LD therapy is due to cumulative effects of LD or to progressive disease. LD-sparing therapy does appear to delay the onset of dyskinesia, but this needs to be weighed against the poorer symptomatic control, and an increase in other troublesome side-effects such as hallucinations. Because of the lack of reliable randomised evidence on which initial therapy is best, there is considerable divergence in clinical opinion and practice. At one end of the spectrum, some clinicians consider that the evidence for LD-sparing therapy is insufficient to justify use of the more expensive and clinically less effective new DAs. Such doctors, who are sceptical about LD toxicity, might consider using LD-sparing therapy only for younger patients for whom the potential for long-term toxicity is a more important consideration. Other clinicians believe that younger patients should be offered LD-sparing therapy on existing evidence but are uncertain whether more elderly patients should be offered LD or LD-sparing therapy. Still others would wish to consider either LD or LD-sparing therapy for their whole range of patients. Other factors, such as the level of disability of patients, are also potential determinants of the appropriateness of different Parkinson's treatment - and, again, there are divergent opinions. Similarly, some doctors are concerned about the safety of selegiline because of the UKPDRG Study and would wish to avoid using it. Others are sceptical about this evidence and believe that this inexpensive drug of proven effectiveness should not be discarded prematurely.

In view of these considerations, the PD MED trial adopts a pragmatic approach with eligibility 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, a particular class of PD drug, then the patient is not eligible for a randomisation including this class of drug (although the patient can still be randomised in one of the two-way randomisation options). If, on the other hand, the doctor is **substantially uncertain** which class of drug a particular patient should be offered, that patient is eligible to be randomised. 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. Eligibility based on uncertainty has been used in many previous trials (e.g. the "ISIS" trials in acute MI, the MRC carotid endarcterectomy trial, and the QUASAR colorectal cancer trial) and has been shown to simplify trial procedures and to facilitate large-scale recruitment of an appropriately heterogeneous group of patients.[20]

3.2. Open label treatment

Blinding of treatment allocation is not considered necessary in PD MED because the potential for subjectively biased assessment is small. There is no reason to expect that patients will have any prior beliefs that one treatment will be better than another (all patients in both randomisations receive active therapy - there are no placebo arms). Likewise the main outcome measures are well-validated, reproducible, patient-rated measures of disability and quality of life.

Moreover, the pragmatic, ‘real life’ design of the trial, which allows clinicians to choose which DA, MAOBI and COMTI to use, and to vary the dose as they see fit, has substantial advantages. The eventual results will be more clinically relevant, in that drug usage will reflect normal clinical

practice which involves frequent dose adjustments to achieve optimal symptom control. Another factor that precludes blinding is the cost of buying, encapsulating and distributing all the drugs for this long-term study, which would be prohibitive. Furthermore, patients with PD will normally obtain their prescriptions from their GPs. Trial procedures are simplified, treatments are given as they would be in normal clinical practice and administrative costs are greatly reduced with open treatment. The substantial advantages of simple, 'real life' procedures that will facilitate large-scale recruitment from many centres, enabling a uniquely large and therefore a uniquely reliable evaluation of the relative merits of different drugs to be undertaken, greatly outweigh the small possibility of assessment bias with open-label treatment.

4. OUTCOME MEASURES

4.1. Patient and carer outcomes

The primary outcomes will be the patient's self-evaluation of their functional status and quality of life (using the PDQ-39 questionnaire) and cost-effectiveness (EuroQoL EQ-5D).

Secondary endpoints will evaluate other aspects of functionality, and safety:

- Cognitive function (MMSE)
- Well being of carers (SF-36)
- Resource usage
- Toxicity and side-effects, including mortality rates
- Time to onset of motor complications (early disease randomisation only) and time to surgical intervention or start of apomorphine (later disease randomisation only)

PDQ-39: A clinically and socially meaningful outcome measure needs to address matters of most concern to the individual with PD. The PDQ-39 (Appendix E) is a patient-completed questionnaire developed by qualitative in-depth interviews involving patients with PD. It includes items that reflect patients' concerns in relation to eight aspects of PD: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily discomfort.[21,22] The instrument has been extensively tested for validity, reproducibility and sensitivity to change in both clinic and population survey applications. For example, the instrument has high convergent and discriminant validity in relation to neurologists' assessments of PD severity using conventional clinical scores, such as Hoehn and Yahr, Columbia and UPDRS, and is sensitive to changes considered of importance to patients, but not identified by clinical ratings.[23,24] It has been translated and used in most European, Australasian and North American countries and has been widely used as an outcome measure in trials of drugs, neurosurgery and nursing care packages.[25]

EuroQoL EQ-5D: The main outcome measure for the economic evaluation will be the EuroQol EQ-5D (Appendix F). Responses will be given valuations derived from published UK population tariffs and the mean number of quality adjusted life-years (QALYs) per patient and incremental QALYs will be calculated. The incremental cost per QALY will then be calculated. All parameters subject to uncertainty will be systematically varied in sensitivity analyses.

ICECAP-O: is a new measure of capability in older people for use in economic evaluation. Unlike most profile measures used in economic evaluations, the ICECAP-O (Appendix P) focuses on wellbeing defined in a broader sense, rather than health. The measure covers attributes of wellbeing that were found to be important to older people in the UK. It will be evaluated to see if it provides an improved sensitivity in outcome measures for patients with PD compared to the EQ-5D.

Cognitive function - **Mini-Mental State Examination (MMSE):** About 10% of PD patients develop dementia. The trial aims to determine whether therapies prevent or decrease the decline of cognitive function - as measured by MMSE (Appendix D) - in PD. MMSE is a well-established 30-point

measure of cognitive function in older people. It is easy to administer, 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. MMSE score is influenced by sociodemographic status but this will even out in a large randomised study. 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 milestone from which patients rarely recover.

Carers
The primary carer should be in at least weekly contact with the patient, preferably co-resident, and should not be someone who is employed as a carer. If there is no suitable carer, or the carer chooses not to participate, the patient can still take part in PD MED.

Carers' psychological well-being: Little work has been done on the effect of anti-Parkinsonian drug prescription on carer attitudes, stress or physical and psychological morbidity. The person identified by the patient as their primary carer will be assessed by the SF-36 (Appendix G), a well-validated measure of health status.

Carer Experience Scale: It is a new profile measure of the caring experience for use in economic evaluation. Unlike most profile measures used in economic evaluations, the CES (Appendix Q) focuses on 'care-related quality of life' rather than health-related quality of life, comprising attributes that are pertinent to unpaid carers.

Side-effects of treatment: The PDQ-39 includes items to assess self-rated severity of PD symptoms. In addition, potential side-effects of drugs, changes to drugs and institutional stays will be assessed by a patient-based instrument developed specifically for the study (Appendix L).

4.2. Resource usage

Direct medical costs: An economic evaluation will be undertaken as part of the trial. Depending on the clinical results of the study, a cost minimisation study (no clinical difference between therapies) or cost-utility analysis (cost per incremental QALY gained) will be performed. Data will be collected from a sample of patients on the volume and type of resources used over the follow-up period. Information on medications, clinic visits, adverse events, hospitalisations and institutionalisation will be collected as an integrated part of the trial case record forms. A sub-sample of patients will be used to estimate the volume and opportunity costs of formal and informal care received by patients. Further details of hospitalisations (main reasons for admission, length of stay) will be collected from the relevant hospitals as required. In addition, patients will be asked at 12-month intervals to complete a simple (one A4 sheet) postal questionnaire covering GP consultations, physiotherapy out-patient visits, hospital stays and other health care resources used over the previous 12 months (Appendix J). All resources used will be costed using current unit costs derived from national statistics and participating centres, and a mean net cost per patient in each trial arm and incremental cost per patient with associated measures of variance will be calculated.

Institutional care: Progression of PD may lead to increased requirements for formal domiciliary or residential care as the limits of informal care are exceeded in some patients. Transitions to more intensive forms of care can be viewed both as outcome and as costs. 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, neurology), followed by individual needs assessment by the Local Authority Social Services (LASS), 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 PD therapies delay these transitions, they may reduce costs. The economic evaluation will adopt a societal perspective including informal and formal costs, i.e. those borne by the NHS and by LASS or privately by patients or their families.

5. TRIAL PROCEDURES: RANDOMISATION

5.1. Eligibility

Eligibility will be based on the uncertainty principle (see Section 3.1). Patients will be eligible if they have a confirmed diagnosis of Parkinson's disease, either early disease (newly/recently diagnosed) or later disease (motor complications).

Early disease randomisation:

Patients are eligible for the early disease randomisation if:

- They are newly or recently diagnosed with Parkinson's disease. It is important to ensure the accurate diagnosis of PD and the UK Brain Bank criteria (Appendix A) should be used.
- They have functional disability requiring medical therapy. Patients not thought to require dopaminergic treatment at diagnosis may be entered once it is considered that such treatment becomes necessary.
- They are previously untreated for PD or have been treated with dopaminergic PD medication for less than 6 months.
- There is no definite contraindication to, or definite indication for, any of the therapies to which they might be allocated. (If it is considered that LD only is not an appropriate option for a patient, they may be randomised two ways between DA and MAOBI. Similarly, if a MAOBI is not considered appropriate, a patient may be randomised two ways between LD and DA.)
- They are able to complete the trial questionnaires. Non-English speaking patients may be entered if they have a carer, relative or other person who can help them fill in the questionnaires, or if translated documentation is available.

Patients are not eligible for the early disease randomisation if:

- They have received previous dopaminergic drug therapy for PD for more than 6 months.
- They are demented (as defined by the medical team responsible).
- They are unable to give informed consent.

Later disease randomisation:

Patients are eligible for the later disease randomisation if:

- They have PD and develop motor complications that are uncontrolled by LD (either alone or in combination with either a DA or a MAOBI) and hence require the addition of another class of drug.
- There is no definite contraindication to, or definite indication for, any of the therapies to which they might be allocated. (Patients who were already receiving a DA when uncontrolled motor fluctuations arose are not eligible for the DA arm and will be randomised between MAOBI and COMTI only. Patients who were receiving a MAOBI when uncontrolled motor fluctuations arose, or for whom the clinician does not wish a MAOBI to be an option, are not eligible for the MAOBI arm and will be randomised between DA and COMTI only.)
- They are able to complete the trial questionnaires. Non-English speaking patients may be entered if they have a carer, relative or other person who can help them fill in the questionnaires, or if translated documentation is available.

Patients are not eligible for the later disease randomisation if:

- They are demented (as defined by the medical team responsible).
- They are unable to give informed consent.

N.B. Patients who have been entered into the early disease randomisation should be re-randomised into the later disease randomisation if motor complications develop that are uncontrolled by drug-dose titration and/or addition of LD if on DA/MAOBI.

5.2. Patient and carer information leaflet

The conduct of the trial will be in accordance with the Medical Research Council policy on ethical considerations. The patient'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 and carer information sheets (Appendix B) and consent form (Appendix C) will be provided so that patients and their carers can find out more about the trial before deciding whether or not to participate.

5.3. Baseline assessments

Once the patient has consented to take part, the MMSE (Appendix D) should be administered. The patient should be asked to complete the PDQ-39 (Appendix E), and EuroQol EQ-5D (Appendix F). The carer, if taking part, should be asked to complete the SF-36 (Appendix G).

5.4. Randomisation

Randomisation notepads (Appendix H) should be used to collate the necessary information prior to randomisation. Complete the baseline assessments as specified in Table 3 overleaf. The person randomising will need to answer all of the questions before a treatment allocation is given. Patients are entered and randomised into the trial by one telephone call to the randomisation service (0800 953 0274 freephone from within the UK or +44 121 415 9127/9128/9129 from outside the UK) or by fax (0121 415 9135 or +44 (0)121 415 9135, from outside the UK). Telephone randomisations are available Monday-Friday, 09:00-17:00 UK time. The patient's GP will need to be notified, and a “specimen letter to GP” is supplied (Appendix I)

6. TRIAL PROCEDURES: TREATMENT AND FOLLOW-UP

6.1. Drug dosages

The pragmatic design of the trial allows clinicians to start treatment with whichever drug they prefer as long as it is within the class of drug (i.e. LD, DA, MAOBI or COMTI) to which the patient was allocated at randomisation. Clinicians can give the chosen drug at the dose and scheduling that they normally use and can titrate the dose as they see fit in the best interests of the patient. Drug dosage information is provided in Appendix N and clinicians are referred to the Summary of Product Characteristics (SPC) for each drug for further details.

6.2. Treatment modifications

If disease symptoms are not adequately controlled by the class of drug allocated, after titrating the dose to the maximum tolerated, then it is permissible, as in usual practice, to add a new agent from another class of drugs. In particular, for patients with early disease allocated to a dopamine agonist or MAOBI, levodopa can be introduced as required. Investigators are encouraged to re-randomise patients whose disease is no longer controlled by the class of drug allocated, even with the addition of levodopa, into the later disease randomisation.

Treatment modifications are also permissible if patients are believed to be experiencing adverse effects from a particular drug. A different drug within the same class is preferable - for example, trying a different dopamine agonist - but an agent from a different class of drug can also be used if considered to be in the patient's best interests. Treatment modifications, and the reason for modification, should be recorded on the follow-up forms.

N.B. For purposes of follow-up and analyses, patients remain in the PD MED study irrespective of treatment compliance. It is important that questionnaires and study documentation are completed for all patients randomised so that unbiased 'intention-to-treat' analyses can be undertaken.

6.3. Other management at discretion of local doctors

Apart from giving out the trial treatments, 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 visits.

6.4. Follow-up assessments

The principal evaluations will be by means of postal questionnaires to be completed by patients and their carers. These patient-based outcome measures (PDQ-39 and EQ-5D) will be collected at base-line, six months, one year and yearly thereafter (see table 3 below). In addition patients' reports of side-effects will be collected at six months, one year and yearly thereafter and resource use data will be collected at one year and yearly thereafter. The trial follow-up involves minimal administration and paperwork on the part of clinicians and their staff. There is just a simple annual questionnaire to clinicians to ascertain changes in disease status (e.g. onset of motor complications) and changes in therapy (Appendix K). MMSE is measured at baseline and at every subsequent 5 years.

6.5. Serious and unexpected adverse events

Treatment-related toxicity with the drugs and dosages employed in the trial is expected to be minor. See Appendix O for potential toxicities, and refer to the Study Product Characteristics for further details. However, to monitor the safety of the drugs used in PD MED, all serious, unexpected adverse events (see footnote A) believed to be due to the PD treatments should be reported to the Trial Office within 48 hours by telephone, e-mail or fax. A detailed report of the event on the Serious Adverse Event Form (Appendix M) should be returned to the Trial Office within 7 days. Adverse events that might reasonably be expected to occur in PD patients receiving the trial treatments do not need to be reported in this way but should be recorded on the annual review form, when this form becomes due.

Dementia

If the patient becomes demented (as defined by the medical team responsible for the patient) then as much data should be collected as practical during the follow-up period using the EQ-5D, Resource Usage Form and an adapted version of the PDQ-39, called the PDQ-17, which may be completed by the carer. These forms will be sent directly to the patient and carer by the Trial Office. Clinical follow-up information will continue to be obtained from the patient's current doctors.

Deaths

A Serious Adverse Event form (Appendix M) and an Annual Follow-up form (Appendix K) should be completed and returned within two weeks if a patient dies. This information will be supplemented by use of national mortality statistics to monitor long-term survival.

Table 3 - Baseline & Follow-up assessments

Assessment	Outcome Measure	Completed by	At Entry	6 Months	1* Year	2* Years	3* Years	4* Years	5* Years
Functional Status/Quality of Life	PDQ-39, EQ-5D, ICECAP-O	Patient	✓	✓	✓	✓	✓	✓	✓
Side effects	Side effect form	Patient		✓	✓	✓	✓	✓	✓
Health Economics	Resource usage	Patient			✓	✓	✓	✓	✓
Carer well-being	SF-36, CES	Carer	✓	✓	✓	✓	✓	✓	✓
Cognitive function	MMSE	Clinician	✓						✓
Disease status	Follow up form	Clinician	Rand. notepad		✓	✓	✓	✓	✓

*Assessment schedule years 1 – 5 repeated for all participants until end of trial December 2019 (ie at least 10 years).

Footnote A "Unexpected" adverse events are defined as those that would not be expected among elderly patients given anti-parkinsonian medication (which has certain expected side-effects) for Parkinson's disease (which has expected symp-toms). For the purposes of this study, **"serious"** adverse events are those which are fatal, life-threatening, disabling or require hospitalisation.

7. SIZE OF DIFFERENCE TO BE MEASURABLE

7.1. Projected accrual

The PD MED study adopts a pragmatic approach to recruitment aiming to include, if possible, 1500 patients in the early disease randomisation and 1000 in the later disease randomisation. These numbers would give very high statistical power (i.e. over 90% power at $p<0.01$) to confirm, or refute, even small differences between the different classes of drugs and, should differences emerge, would also be enough to allow meaningful exploration of any differences in the size of benefit between different types of patient, between particular drugs within a class, or over time.

The minimum clinically meaningful difference used for sample-size calculations is 6 points on the PDQ-39 mobility scale. This 6-point difference is based on a study of patients attending neurology clinics with PD who completed the PDQ-39 at base-line and four months later and were also asked to complete 'transition questions' at follow-up. Patients who rated themselves as worse at follow-up, whether in terms of a transition item on physical function or an item on their PD generally, experienced a mean deterioration of 7 points on the PDQ-39 mobility scale.[20] A 6-point change is used in PD MED because it translates more easily into meaningful categories, both of health states and health changes. The mobility scale has 10 items with 5 response categories (ranging from 'never' to 'always') and scores ('0' to '4') are transformed to produce a range 0-100. A 6-point change therefore results if a respondent changes three categories on one item, for example from 'being con-fined to the house - never' to 'being confined to the house - often'. The same change in score would also result from changing one response category - for example, from 'sometimes' to 'often' - on three of the ten items.

The main analyses in PD MED will compare changes from baseline in PDQ-39 score between groups. The standard deviation (SD) between patients of the 1-year changes in the PDQ-39 mobility dimension in early PD MED data is 18.6. This estimate appears robust, as the SD is about the same for 6-month change and for patients in the early and late randomisations, but is smaller - as, consequently, is the sample size - than the original protocol estimate of 31.6. The earlier estimate was larger because it was based on the between-patient SD seen in an unselected series of neurological clinic attendees with PD. To detect a 6-point difference (i.e. a standardised difference of $6/18.6 = 0.32$) with 90% power at $p<0.01$ would require 300 patients in each arm. 155 patients in each arm would give 80% power at $p<0.05$. Thus, although it will be highly desirable for PD MED to randomise a total of 1500 early PD patients and 1000 later PD patients - to improve precision of treatment estimates and for more meaningful subgroup investigations - the study would still have good statistical power to detect small differences with about half as many patients, although subgroup analyses would then only be possible if the treatment differences were of moderate size.

Large-scale recruitment to PD MED should be feasible. There are at least 8,000 new cases of PD diagnosed in the UK each year. If just 5-6% of these were to be randomised between the early PD treatment options, then 1500 patients could be randomised in just 3-4 years. If only 3% of patients were to be entered, 900 could be randomised in the same time scale. The number of patients available for the later disease randomisation should be comparable as most patients diagnosed with PD eventually develop motor complications requiring treatment modifications. The majority of these patients are likely to have received only prior LD, so would be potentially eligible for randomisation between all 3 arms. Some patients (perhaps 20%) will have been previously treated with either a DA or MAOBI, and will only be randomised between MAOBI versus COMTI (if previous DA exposure) or between DA versus COMTI (if previous MAOBI exposure). To recruit 300 patients in each arm, about 1000 patients will need to be randomised (perhaps approximately: DA 300, MAOBI 300, COMTI 400). Again, the study would have good statistical power to detect small differences with about half as many patients.

7.2 Treatment comparisons

In the semi-factorial early disease randomisation, there will be two pre-specified comparisons:

1. LD-sparing therapy (either DA or MAOBI) versus LD alone, to determine whether LD-sparing therapy is better than LD alone.
2. DA versus MAOBI, to determine which form of LD-sparing therapy is the better.

In the later disease randomisation, there will also be two pre-specified comparisons:

3. DDI (either MAOBI or COMTI) vs DA, to determine whether DDI or DA is better.
4. COMTI versus MAOBI, to determine which form of DDI is the better.

Should one class of LD-sparing therapy or one class of DDI be clearly better than the other, then this drug class will be compared with LD alone in early disease or DA in later disease respectively.

7.3. Stratification variables

The early disease randomisation will be 'minimised' within strata defined by whether or not the patient has received previous LD therapy (none, up to one month, one to three months, three to six months), disease stage (Hoehn & Yahr stage - see Randomisation Notepad - Appendix A, for definitions) and by age (<50, 50-59, 60-69, 70-79, 80+ years). Prior hypotheses will be that younger patients and LD-naïve patients derive greater net benefit from LD-sparing therapy. The later disease randomisation will be minimised by age, disease stage (as above) by previous therapy (LD only, DA, MAOBI, COMTI), and by time from initial diagnosis of PD to entry (<4 years, 4-6 years, 6+ years). Subgroup analyses within randomisation strata will be undertaken. Indirect comparisons between types of DA, MAOBI and COMTI will be used to generate hypotheses for prospective testing, rather than to provide definitive answers. Because of the serious dangers of misinterpretation, all subgroup analyses will be interpreted appropriately cautiously.

7.4. Data Monitoring Committee: determining when clear answers have emerged

If any of the Parkinson's disease therapies being tested really are substantially better or worse than the others with respect to the main endpoints, or survival, then this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge that particular drugs are definitely more, or less, effective than all, or some of, those used in the trial. 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 DMC may request. The DMC will advise the chair of the Trial Steering Committee if, in their view, any of the randomised comparisons in the trial have provided both (a) "proof beyond reasonable doubt" (see footnote B) that for all, or for some, types of patient one particular treatment is definitely indicated or definitely contraindicated in terms of a net difference in the primary outcome measures, 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 close or modify any part of the trial.

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 unaware 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 PD MED Trial Office to the chair of the DMC, 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.

Footnote B : 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.

8. ORGANISATION

To ensure the smooth running of the trial, and to conform with research governance requirements, it is proposed that each participating centre should designate individuals who would be chiefly responsible for local coordination of clinical and administrative aspects of the trial.

8.1. Principal Investigator at each centre

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

Acting as lead clinician for Local Research Ethics Committee (LREC) and Trust approvals for the trial on behalf of their centre: (See Section 8.4.) Once all necessary approvals have been gained, the Trial Office will send a folder containing all trial materials to the Principal Investigator. Screening and recruitment of patients into the trial can then begin.

To ensure that all medical and nursing staff involved in the care of Parkinson's disease are well informed about the study: This involves distributing 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 regularly updated PowerPoint presentation will be provided for each hospital so that they can be shown from time to time, especially to new staff.

Chief nursing co-ordinator at each centre: It is suggested that each participating centre should designate one nurse as local nursing co-ordinator. This person would be responsible for ensuring that all eligible patients are considered for the study, that patients are provided with study information sheets, and have an opportunity to discuss the study if required. The nurse may be responsible for collecting the patient consent form, baseline PDQ-39, EuroQoL EQ-5D, MMSE and SF36 questionnaires. Again, this person would be sent updates and newsletters, and would be invited to training and progress meetings.

8.2. Central co-ordination

The PD MED Trial Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for providing the trial folders containing all trial materials. These will be supplied to each collaborating centre, after relevant ethics committee approval has been obtained. Additional supplies of any printed material can be obtained on request. The Trial Office also provides the central randomisation service and is responsible for collection and checking of data (including reports of serious adverse events thought to be due to trial treatment) and for analyses.

8.3. Cost implications

The trial has been designed to minimise extra costs for participating hospitals. No extra visits to hospital need to be made, and no extra tests are required. The only extra work involved for participants will be informing patients about the study, obtaining their consent to participate, providing baseline data at randomisation, and reporting, infrequently, their progress. Centres can obtain extra support for this work from the NHS Research Support budget and the Trial Office will help them do this. Allowing clinicians to choose whichever DA, MAOBI or COMTI that they would use in their usual daily practice, means that the trial should not involve additional drug costs. Indeed, it could lead to wider use of LD and selegiline, which are considerably less expensive than any of the newer drugs, and thus could lead to substantial future cost savings if LD or selegiline are shown to be of equal or greater efficacy than the newer DAs or COMTIs.

8.4. Research Governance

The University of Birmingham is the sponsor of the PD MED trial. It has Multi-centre Research Ethics Committee (MREC) approval and Clinical Trials Authorisation from the Medicines and Healthcare Regulatory Authority (MHRA). The Trial Office will assist the Principal Investigator to obtain a site specific assessment from the local research ethics committee (LREC) and approval from the Hospital Trust.

The study will adopt a centralised approach to monitoring data quality and compliance. A computer database will be constructed specifically for the study data and will include range and logic checks to prevent erroneous data entry. The trial statistician will regularly check the balance of allocations by the stratification variables. Source data verification will only be employed if there is reason to believe data quality has been compromised, and then only in a sub-set of practices.

8.5. Indemnity

There are no special arrangements for compensation for non-negligent harm suffered by patients as a result of participating in the study. PD MED is not an industry-sponsored trial and so ABPI guide-lines on indemnity do not apply. The manufacturers of the various PD therapies have not been involved in any way in the design or conduct of the trial. The normal NHS indemnity arrangements for non-negligent liability in clinician-initiated research will therefore operate. It should be noted that NHS Trust and non-Trust hospitals are responsible for any negligent liability because of their duty of care to a patient being treated within their hospital, whether or not that patient is participating in a clinical trial.

8.6. 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 the study 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, who will be listed as co-authors.

It is requested that any proposals for formal additional studies of the effects of the trial treatments on some 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.

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10. Questionnaires, Information Sheets, Consent Forms and other forms and information set out as Appendices

Appendix A	UK Brain Bank diagnostic criteria for PD & Hoehn & Yahr Stages
Appendix B	Patient Information Sheet for Early and Later Disease
Appendix C	Patient & Carer Consent Form
Appendix D	Mini-Mental State Examination (MMSE)
Appendix E	PDQ-39 Questionnaire
Appendix F	EuroQol EQ-5D
Appendix G	SF-36
Appendix H	Randomisation Notepad
Appendix I	GP Letter
Appendix J	Resource Usage
Appendix K	Annual Follow-up Form for Early and Later Disease
Appendix L	Side Effect Form
Appendix M	Serious Adverse Event Form
Appendix N	Availability & Dosage of Drugs
Appendix O	Toxicity of Drugs
Appendix P	ICECAP-O
Appendix Q	Carer Experience Scale

PD MED TRIAL SCHEMA

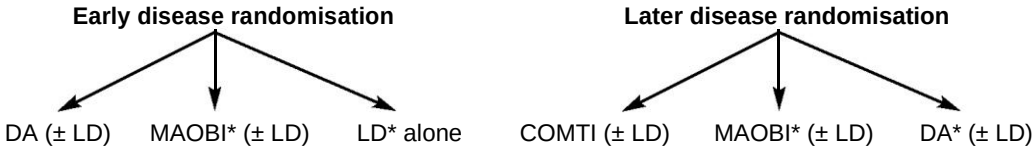
ELIGIBILITY

Early disease randomisation: Patients with newly or recently diagnosed PD (Note A) requiring medical therapy. No prior, or less than 6 months, treatment with PD medication.
Later disease randomisation: Patients with PD who develop motor complications that are uncontrolled by their current therapy: either levodopa (LD) alone or LD with the addition of a dopamine agonist (DA) or a monoamine oxidase type B inhibitor (MAOBI).
Both randomisations: Patient not demented, able to give informed consent and able to complete questionnaires.

Note A: See Appendix A for diagnostic criteria for PD

RANDOMISATION

Randomisation is based on the "uncertainty principle". That is, if there is a definite indication for, or a definite contraindication against, a particular class of drug, then the patient is not eligible for a randomisation that includes this class of drug (Note B). If, however, the doctor is substantially uncertain which class of drug a patient should be offered, that patient is eligible to be randomised. Options are (Note C):



*optional arm

Note B: If one class of drug is contra-indicated the patient can still be randomised two-ways between the other two classes in both early and later disease (see protocol sections 2.2 and 2.3)

Note C: A patient who was initially entered into the early disease randomisation may also be entered into the later disease randomisation if motor complications subsequently develop

TELEPHONE RANDOMISATION

Obtain patient's consent (Appendix C).
Administer baseline assessments (section 5.3)
Prepare for telephone questions using the randomisation notepad (see Note D).
Telephone or fax the randomisation service (contact details below).
When all the relevant questions on the randomisation notepad have been answered, a treatment allocation and patient reference number will be given.

Note D: The person randomising will need to answer all questions on the randomisation notepad (Appendix H).

TREATMENT

The patient should be prescribed the class of drug to which they were allocated at randomisation.
The specific drug used within this class, and drug dose and schedule, is up to each clinician's preference and local practice (Note E).
All other management is as considered appropriate by the responsible physicians.

Note E: Guidelines are provided in Appendix N and clinicians are referred to the Summary of Product Characteristics for further information.

FOLLOW-UP

The majority of assessments will be patient (or carer) based, with postal questionnaires at 6 months and 1 year after entry, then annually (see section 6.4)
Once a year, clinicians will be asked to fill in a simple form giving details of any changes in disease status or therapies used.

FOR RANDOMISATION, TELEPHONE (FREEPHONE IN UK): 0800 953 0274
OR +44 (0)121 415 9129 FROM OUTSIDE THE UK OR FAX 0121 415 9135
For queries and trial supplies, contact the PD MED Trial Office, University of Birmingham Clinical Trials Unit, Robert Aitken Institute, Division of Medical Sciences, Vincent Drive, Edgbaston, Birmingham B15 2TT
Tel: 0121 415 9127/9128/9129

PD MED PROTOCOL APPENDICES

Protocol Version 8 August 2010

Questionnaires, Information Sheets, Consent Forms and other forms and information set out as Appendices

All the forms reproduced here are available from the PD MED Trial Office in either paper or in electronic form as PDF files. They are also available on the PD MED Web site at http://www.pdmed.bham.ac.uk

FOR RANDOMISATION TELEPHONE (FREEPHONE IN UK): 0800 953 0274
OR +44 (0)121 415 9129 FROM OUTSIDE THE UK OR FAX 0121 415 9135
For administrative queries and trial supplies, contact the PD MED Trial Office, University of Birmingham Clinical Trials Unit, Robert Aitken Institute, Vincent Drive, Edgbaston Birmingham B15 2TT Tel: 0121 415 9127/9128
E-mail: pd-trials@bham.ac.uk Website: www.pdmed.bham.ac.uk

Appendix A

UK BRAIN BANK DIAGNOSTIC CRITERIA FOR PD

STEP 1. Diagnosis of Parkinsonian syndrome

Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) and at least one of the following:

- muscular rigidity
- 4-6 Hz rest tremor
- postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction.

STEP 2. Exclusion criteria for Parkinson's disease

- history of repeated strokes with stepwise progression of Parkinsonian features
- history of repeated head injury
- history of definite encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after three years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language and praxis
- Babinski sign (Plantar Reflex)
- presence of a cerebral tumour or communicating hydrocephalus on CT scan
- negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure

STEP 3. Supportive prospective positive criteria for Parkinson's disease; three or more required for diagnosis of definite Parkinson's disease

- unilateral onset
- rest tremor present
- progressive disorder
- persistent asymmetry affecting the side of onset most
- excellent response (70-100%) to levodopa
- severe levodopa-induced chorea
- levodopa response for 5 years or more
- clinical course of 10 years or more

UK Parkinson's Disease Society Brain Bank diagnostic criteria for idiopathic Parkinson's disease.

From: Gibb WRG, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. Journal of Neurology Neurosurgery and Psychiatry 1988; 51: 745-752.

Hoehn and Yahr Stages

Stage 1.0 Unilateral involvement only
Stage 1.5 Unilateral and axial involvement
Stage 2.0 Bilateral involvement without impairment of balance
Stage 2.5 Mild bilateral involvement with recovery on retropulsion (pull) test
Stage 3.0 Mild to moderate bilateral involvement, some postural instability but physically independent
Stage 4.0 Severe disability, still able to walk and to stand unassisted
Stage 5.0 Wheelchair bound or bedridden unless aided.

Appendix B

Patient & Carer Information Sheet
Invitation to join a national study of drug treatment for early Parkinson's disease

In Collaboration with this Hospital and Health Trust

For further information please contact:	
Dr	Tel:
Nurse	Tel:

We would like to invite you to take part in a large national research study, called PD MED, of treatments for Parkinson's disease (PD for short). This study is optional so you don't have to take part if you don't want to, or give a reason if you choose not to. Before you decide, it is important for you to understand why the study is being done and what it involves. Please take time to read the following information and to discuss it with your family, friends and GP as you wish.

Why have I been invited?

Your hospital consultant is taking part in this study, which compares different drugs for PD. Patients are invited to take part if they have recently been diagnosed as having PD, and have not been taking medication for PD for more than 6 months. You are in this group and so are eligible to participate, should you choose to do so.

What is Parkinson's disease?

PD is a movement disorder that affects various parts of the body, causing stiffness in the muscles, slowness, difficulty when starting movements, and tremor in some people. This is caused by a reduction in the numbers of brain cells that produce a chemical called dopamine. These symptoms appear over many years but drug treatments can help slow the effects of this process.

What treatment is there for Parkinson's disease?

There are three main classes of drug (called levodopa, dopamine agonists, and MAOB inhibitors) that can be used to treat the symptoms of early PD, and within each class there may be more than one drug available. We know from previous studies that each of these classes of drug can be effective at controlling symptoms of PD and all of these treatments are widely used, with some doctors preferring one type and other doctors another.

If these treatments are all effective why do we need a clinical trial?

Although we know that these drugs do work, little is known about how they compare with each other and whether or not some drugs are better than others. This is because few studies have directly compared one class of drug with another. Also, most previous studies have just looked at PD symptoms, and side effects of treatments, and have not asked people with PD what the overall impact of the drugs on their daily life (and their carers') has been. We know that there will not be big differences between one class of drug and another but it is possible that some will be a little better than others. The only way that we can find this out reliably is through large clinical studies like PD MED (which aims to recruit up to 1500 patients similar to you). PD is, unfortunately, a common condition and so it is important to make sure that all new drugs really are better than the standard drugs before they also become standard treatment. This means weighing up all the advantages and disadvantages of each type of drug - in what is called a clinical trial - and seeing which is best overall from the patients' point of view. This is what we hope to find out from the PD MED study.

Which patients will get which class of drug?

Since we do not know which class of drug is best, we need to compare them to find out. In order to do this, patients who agree to take part in the study will be allocated to one of the three treatment groups below. The decision as to which group patients are assigned to is made at random by the central study office. The three drug classes being compared are:

- dopamine agonists (these increase dopamine-type stimulation in the brain)
- MAOB inhibitors (this stands for monoamine oxidase type B inhibitor and these drugs work by reducing the breakdown of dopamine in the brain)
- levodopa (the standard drug for many years)

Patients for whom any one of these three classes of drug would be suitable would have an equal chance of being allocated to each group. However, if your doctor considers that one particular drug type would not be appropriate for you, you would only be allocated between the other two groups, and you would then have a 50:50 chance of receiving either one of the other drug class. [If your doctor thinks that only one of these three classes of drug would be suitable for you, he would give you this drug and you would not be eligible for the study.]

If more than one drug is available within the class to which you are allocated, your doctor will choose which one to give you. He would also use the drug at the dose that suits you best. If you are allocated either a dopamine agonist or a MAOB inhibitor, your doctor may also add in levodopa if this is thought to be necessary. Whatever drug, or drugs, you receive during the study, you will still have access to the same medical and nursing support that would be provided if you were not in the study.

What does the PD MED Study involve?

The study involves taking the drug, or drugs, allocated regularly as prescribed by your hospital doctor or GP. Your doctor will explain how and when the drugs should be taken. It is important that you tell your doctor of any changes in your symptoms so that the dosage of the drugs can be adjusted as necessary.

No extra physical tests or clinic visits are necessary as part of the study. Patients will visit their hospital doctor as usual. Each patient will be asked to complete a straightforward set of questions when they enter the study, 6 months later, 12 months later and then once a year for at least another 4 years. Your carer, if you have one, will also be asked to answer some questions so that we can find out how helping to look after someone with PD affects their life. These questionnaires will be sent to you, and your carer, by post and a postage-paid envelope will be provided for their return. It should not take more than half an hour to complete them each time. We will also ask your doctors about once a year how you are progressing.

All information collected in the study will be put into a computer and analysed, but will remain strictly confidential in the same way as your other medical records. You will not be identified when the results are reported. Your GP will need to be told that you are taking part in the study as he/she usually supplies your prescriptions.

What are the risks of taking these drugs?

Doctors generally agree that all the drugs prescribed in this study are safe but, as with any treatment, we cannot guarantee that there will be no side effects. Your doctors will tell you about the possible side effects of the treatments that you might receive. It is important that you tell your doctors if the study drugs cause upsets so that they can decide whether other treatment is required or the drug needs to be stopped. If new information about the drugs you are taking comes to light during the course of the study, your doctors will tell you about it and discuss with you whether you should continue or change your treatment.

Are there any benefits for me from taking part in the study?
All of the treatments being used in this study are known to help control the symptoms of PD and are already widely used, so the treatment you receive will be at least as good as that available outside the study. We hope that the information obtained from this study will help us to treat people with PD more effectively in the future.

What will happen to the results of the study?
At the end of the study your questionnaires, and those from others taking part, will be analysed and a report written for a leading medical journal. The NHS will help ensure that UK doctors are aware of the results, so that patients can be treated with the best proven, effective treatments.

Will participation in the study affect my legal rights?
No. There are no special arrangements for compensation in the (unlikely) event that you are harmed as a result of taking part in the study. But, whether or not you take part, you will retain the same legal rights as any other patient treated in the NHS.

Who is organising and funding the study?
The central study organiser is the University of Birmingham Clinical Trials Unit, which has experience of running large trials like PD MED. The study is funded by the NHS Research & Development Programme. The doctors involved are not being paid for recruiting patients into the study. The study has also been reviewed by the West Midlands Multi-centre Research Ethics Committee and the Local Research Ethics Committee at your hospital.

Do I have to take part in the study?
No, you do not have to take part in the study, or give a reason if you choose not to, and this would not affect the standard of care that you receive. It is up to you to decide. Before deciding, you should read this leaflet carefully and ask your doctor or nurse questions if there are things that you do not understand. If you do decide to take part, we will ask you, and your carer if you have one, to sign a consent form indicating that you understand what the study involves and agree to take part. You will be given a copy of this information sheet and the signed consent form to keep. Your hospital doctor will then call the study organisers to enter you into PD MED.

Can I withdraw from the study?
Yes, you can decide to withdraw from the study at any time. Signing the consent form does not commit you to taking the treatment allocated and withdrawal will not affect the standard of care that you receive subsequently. If you do change your mind later you do not have to give a reason, but it would help our research if you could still complete the questionnaires to let us know how you are doing.

Do you have any other questions?
Having read this leaflet we hope that you will choose to take part in PD MED. If you would prefer to delay your decision, perhaps to discuss with friends, relatives or your GP, then you can make an appointment to come back later. You can take this information sheet with you to help you decide. If you still have questions about the study now or later feel free to ask your hospital doctor or nurse.
Their names and telephone numbers are given at the top of this sheet.

Thank you for taking the time to consider participating in this study.

More information can be found about PD MED from the web site
http://www.pdmed.bham.ac.uk/

Patient & Carer Information Sheet
Invitation to join a national study of drug treatment for later Parkinson's disease

Appendix B

In Collaboration with this Hospital and Health Trust

For further information please contact:	
Dr	Tel:
Nurse	Tel:

We would like to invite you to take part in a large national research study, called PD MED, of treatments for Parkinson's disease (PD for short). This study is optional so you don't have to take part if you don't want to, or give a reason if you choose not to. Before you decide, it is important for you to understand why the study is being done and what it involves. Please take time to read the following information and to discuss it with your family, friends and GP as you wish.

Why have I been invited?
Your hospital consultant is taking part in this study, which compares different drugs for PD. Patients are invited to take part if their current therapy is not working well enough and so their treatment needs to be changed. You are in this group and so are eligible to participate, should you choose to do so.

Why does my treatment need to be changed?
The drugs that you have been taking until now are no longer able to control the symptoms as well as before. It is possible that changing to other drugs will be better. There are three different classes of drugs (called dopamine agonists, MAOB inhibitors and COMT inhibitors) that can be used at this stage to treat the symptoms of PD, and within each class there may be more than one drug available. We know from previous studies that each of these classes of drug can be effective at controlling symptoms of PD and all of these treatments are widely used, with some doctors preferring one type and other doctors another.

If these treatments are all effective why do we need a clinical trial?
Although we know that these drugs do work, little is known about how they compare with each other and whether or not some drugs are better than others. This is because few studies have directly compared one class of drug with another. Also, most previous studies have just looked at PD symptoms, and side effects of treatments, and have not asked people with PD what the overall impact of the drugs on their daily life (and their carers') has been. We know that there will not be big differences between one class of drug and another but it is possible that some will be a little better than others. The only way that we can find this out reliably is through large clinical studies like PD MED (which aims to recruit up to 1000 patients similar to you). PD is, unfortunately, a common condition and so it is important to make sure that all new drugs really are better than the standard drugs before they also become standard treatment. This means weighing up all the advantages and disadvantages of each type of drug - in what is called a clinical trial - and seeing which is best overall from the patients' point of view. This is what we hope to find out from the PD MED study.

Which patients will get which class of drug?

Since we do not know which class of drug is best, we need to compare them to find out. In order to do this, patients who agree to take part in the study will be allocated to one of the three treatment groups below. The decision as to which group patients are assigned to is made at random by the central study office. The three drug classes being compared are:

- dopamine agonists (these increase dopamine-type stimulation in the brain)
- MAOB inhibitors (this stands for monoamine oxidase type B inhibitor and these drugs work by reducing the breakdown of dopamine in the brain)
- COMT inhibitors (this stands for catechol-O-methyltransferase inhibitor and these drugs work by reducing the breakdown of levodopa in the brain).

Patients who have previously been treated with levodopa would have an equal chance of receiving any one of these three classes of drug. However, if you have previously been taking either a dopamine agonist or a MAOB inhibitor (or if your doctor considers that one of these drugs would not be appropriate for you), you will only be allocated between the other two groups, and you would then have a 50:50 chance of receiving either one of them. [If your doctor thinks that only one of these three classes of drug would be suitable for you, he would give you this drug and you would not be eligible for the study.]

If more than one drug is available within the class to which you are allocated, your doctor will choose which one to give you. He would also use the drug at the dose that suits you best. Your doctor may also add in levodopa if this is thought to be necessary. Whatever drug, or drugs, you receive during the study, you will still have access to the same medical and nursing support that would be provided if you were not in the study.

What does the PD MED Study involve?

The study involves taking the drug, or drugs, allocated regularly as prescribed by your hospital doctor or GP. Your doctor will explain how and when the drugs should be taken. It is important that you tell your doctor of any changes in your symptoms so that the dosage of the drugs can be adjusted as necessary.

No extra physical tests or clinic visits are necessary as part of the study. Patients will visit their hospital doctor as usual. Each patient will be asked to complete a straightforward set of questions when they enter the study, 6 months later, 12 months later and then once a year for at least another 4 years. Your carer, if you have one, will also be asked to answer some questions so that we can find out how helping to look after someone with PD affects their life. These questionnaires will be sent to you, and your carer, by post and a postage-paid envelope will be provided for their return. It should not take more than half an hour to complete them each time. We will also ask your doctors about once a year how you are progressing.

All information collected in the study will be put into a computer and analysed, but will remain strictly confidential in the same way as your other medical records. You will not be identified when the results are reported. Your GP will need to be told that you are taking part in the study as he/she usually supplies your prescriptions.

What are the risks of taking these drugs?

Doctors generally agree that all the drugs prescribed in this study are safe but, as with any treatment, we cannot guarantee that there will be no side effects. Your doctors will tell you about the possible side effects of the treatments that you might receive. It is important that you tell your doctors if the study drugs cause upsets so that they can decide whether other treatment is required or the drug needs to be stopped. If new information about the drugs you are taking comes to light during the course of the study, your doctors will tell you about it and discuss with you whether you

Are there any benefits for me from taking part in the study?
All of the treatments being used in this study are known to help control the symptoms of PD and are already widely used, so the treatment you receive will be at least as good as that available outside the study. We hope that the information obtained from this study will help us to treat people with PD more effectively in the future.

What will happen to the results of the study?
At the end of the study your questionnaires, and those from others taking part, will be analysed and a report written for a leading medical journal. The NHS will help ensure that UK doctors are aware of the results, so that patients can be treated with the best proven, effective treatments.

Will participation in the study affect my legal rights?
No. There are no special arrangements for compensation in the (unlikely) event that you are harmed as a result of taking part in the study. But, whether or not you take part, you will retain the same legal rights as any other patient treated in the NHS.

Who is organising and funding the study?
The central study organiser is the University of Birmingham Clinical Trials Unit, which has experience of running large trials like PD MED. The study is funded by the NHS Research & Development Programme. The doctors involved are not being paid for recruiting patients into the study. The study has also been reviewed by the West Midlands Multi-centre Research Ethics Committee and the Local Research Ethics Committee at your hospital.

Do I have to take part in the study?
No, you do not have to take part in the study, or give a reason if you choose not to, and this would not affect the standard of care that you receive. It is up to you to decide. Before deciding, you should read this leaflet carefully and ask your doctor or nurse questions if there are things that you do not understand. If you do decide to take part, we will ask you, and your carer if you have one, to sign a consent form indicating that you understand what the study involves and agree to take part. You will be given a copy of this information sheet and the signed consent form to keep. Your hospital doctor will then call the study organisers to enter you into PD MED.

Can I withdraw from the study?
Yes, you can decide to withdraw from the study at any time. Signing the consent form does not commit you to taking the treatment allocated and withdrawal will not affect the standard of care that you receive subsequently. If you do change your mind later you do not have to give a reason, but it would help our research if you could still complete the questionnaires to let us know how you are doing.

Do you have any other questions?
Having read this leaflet we hope that you will choose to take part in PD MED. If you would prefer to delay your decision, perhaps to discuss with friends, relatives or your GP, then you can make an appointment to come back later. You can take this information sheet with you to help you decide. If you still have questions about the study now or later feel free to ask your hospital doctor or nurse. Their names and telephone numbers are given at the top of this sheet.

Thank you for taking the time to consider participating in this study.
More information can be found about PD MED from the web site
http://www.pdmed.bham.ac.uk/

A LARGE RANDOMISED ASSESSMENT OF THE RELATIVE COST-EFFECTIVENESS OF CLASSES OF DRUGS FOR PARKINSON'S DISEASE

In Collaboration with this Hospital and Health Trust

For further information please contact:

Dr Tel:

Please tick each box to indicate your consent

- I have been informed about the **PD MED** study and agree to enter it. I hope to complete the study, but I understand that I am free to withdraw from the study at any time without necessarily giving a reason. If I do withdraw, I can continue to expect the highest standard of care from my doctors. ☐
- I understand that my doctors will provide information about my progress, in confidence, to the central organisers and that the information held by the NHS and records maintained by the General Register Office may be used to keep in touch with me and follow up my health status. ☐
- I understand that the information will be used for medical research only and that I will not be identified in any way in the analysis and reporting of the results. ☐
- I understand that my carer, if I have one, will be asked to provide information on how looking after someone with Parkinson's disease affects their life. ☐
- I consent to my GP being informed about my participation in this study. ☐

Patient's signature: _____

Print full name: _____ Date: / / 200

Carer's Consent *(if applicable)*:

I have also been informed about the **PD MED** study and agree to take part and to provide information about how the patient's disease affects me.

Carer's signature: _____

Print full name: _____ Date: / / 200

Clinician's signature: _____

Print name: _____ Date: / / 200

*Three copies of this consent form are needed: **the top** (white) **copy** to be kept in the patient notes ; pink copy for the patient; blue copy for the carer (if applicable); yellow copy to be sent to the **PD MED** Trial office .*

A Freepost envelope is supplied for return to
The University of Birmingham, Birmingham Clinical Trials Unit, **FREEPOST RRKR-JUZR-HZHG**, Birmingham B15 2TT

Mini-Mental State Examination (MMSE)

Baseline / 5 Year follow-up (please circle as appropriate)

	Score
1. Orientation Say - **Can you tell me the date?** Ask specifically for any items omitted (day, date, month, season, year). Allow flexibility when the season changes. Score one point for each correct answer. Score 0-5	
Say - **Can you tell me the name of this place?** What town/city, county, country are we in? What floor of the building are we on? (check meaning of first and ground floor). Score one point per correct answer. Score 0-5	
2. Registration Say - **I would like to test your memory. I want you to remember three things - apple, table, penny** (say items clearly and slowly allowing one second between each item). Say - **Can you repeat them?** First repetition determines score, one point for each exactly correct answer. Score 0-3	
3. Attention and Calculation Say - **Start with 100 and keep taking 7 away until I tell you to stop.** (Continue to 5 subtractions). Score a point when patient successfully subtracts seven even if previous number was wrong. If patient cannot or will not perform the task, test reverse spelling. Say - **I would like you to spell `WORLD' backwards.** Score the number of letters in the correct order (D=1, L=1, R=l, 0= 1, W=1). Score 0-5	
4. Recall Say - **Can you tell me the three things that I asked you to remember?** (apple, table and penny). Allow ten seconds for reply. Give one point for each exactly correct answer. Score 0-3	
5. Naming Accurate naming is required; descriptions of function or approximate answers are unacceptable. Show the patient a wristwatch and ask - **What is this?** Score one point for either watch, wristwatch or time-piece. Score 0-1	
Show the patient a pencil and ask - **What is this?** Score one point for pencil only. If approximate answer is given say - **Can you think of another word for this?** Score 0-1	
6. Repetition Say - **Listen carefully and repeat what I say, `No ifs ands or buts'.** Read phrase slowly and clearly enunciating all the S's. Score one point for correct phrase. Score 0-1	
7. Three stage command Say - **Take this piece of paper in your right hand, fold it in half using both hands and put it on the floor.** Hand A4 piece of paper to patient's mid-line, allow 30 seconds, score one point for each correct stage completed in the correct order. Do not coach or repeat instructions. Score 0-3	
8. Reading Comprehension Show the patient the statement "**Close your eyes**", (written overleaf). Say - **Read this and do what it says**. Repeat instructions if necessary. Score one point if patient closes eyes. Score 0-1	
9. Writing Give the patient a pen and the reverse side of this sheet. Say - **Write a sentence on this piece of paper**, **(anything will do as long as it makes sense).** If the patient does not appear to understand, repeat instructions. Score one point if there is a subject and a verb, correct spelling, grammar and punctuation are not necessary. Allow 30 seconds to complete task. Score 0-1	
10. Praxis Show the intersecting pentagons overleaf. Say-**Copy this shape**. Score one point if there are five sides and five angles on each pentagon, and the overlap forms a diamond. Ignore tremor and rotation. Allow up to one minute and patient may be allowed multiple attempts. Score 0-1	
TOTAL SCORE	

CONSCIOUSNESS Estimate by marking on the line patient's conscious level on a continuum from fully alert on the left to coma on the right. This does not contribute to the total score. **Alert** **Drowsy** **Stupor** **Coma**

Name of person administering MMSE _____ **Date** _____

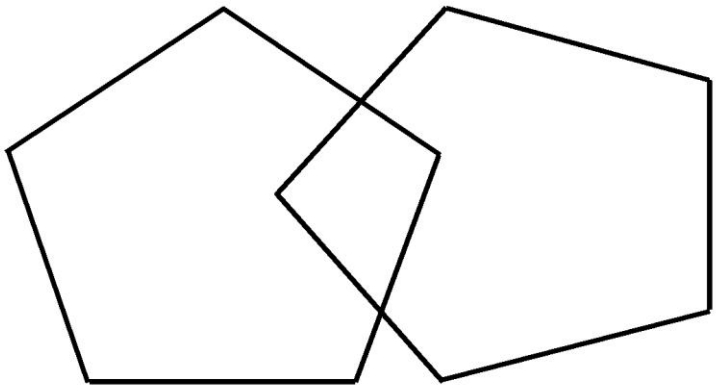
Please complete the following
PD MED Trial Number

Patient Initials: .....
Date of Birth: ..... / ..... / .....
Date Completed: ..... / ..... / .....

Trial office use only
Date Sent: ..... / ..... / .....
Date Received: ..... / ..... / .....
Date Entered: ..... / ..... / .....

Appendix D

Close your eyes



PDQ-39 QUESTIONNAIRE

Please complete the following

Please tick one box for each question

Due to having Parkinson's disease, how often during the last month have you....		**Never**	**Occasionally**	**Sometimes**	**Often**	**Always** or cannot do at all
1	Had difficulty doing the leisure activities which you would like to do?	☐	☐	☐	☐	☐
2	Had difficulty looking after your home, e.g. DIY, housework, cooking?	☐	☐	☐	☐	☐
3	Had difficulty carrying bags of shopping?	☐	☐	☐	☐	☐
4	Had problems walking half a mile?	☐	☐	☐	☐	☐
5	Had problems walking 100 yards?	☐	☐	☐	☐	☐
6	Had problems getting around the house as easily as you would like?	☐	☐	☐	☐	☐
7	Had difficulty getting around in public?	☐	☐	☐	☐	☐
8	Needed someone else to accompany you when you went out?	☐	☐	☐	☐	☐
9	Felt frightened or worried about falling over in public?	☐	☐	☐	☐	☐
10	Been confined to the house more than you would like?	☐	☐	☐	☐	☐
11	Had difficulty washing yourself?	☐	☐	☐	☐	☐
12	Had difficulty dressing yourself?	☐	☐	☐	☐	☐
13	Had problems doing up buttons or shoe laces?	☐	☐	☐	☐	☐

*Please check that you have ticked **one box for each question** before going on to the next page*

Due to having Parkinson's disease, how often <u>during the last month</u> have you....		***Please tick <u>one</u> box for each question***				
		Never	**Occasionally**	**Sometimes**	**Often**	**Always** or cannot do at all
14	Had problems writing clearly?	☐	☐	☐	☐	☐
15	Had difficulty cutting up your food?	☐	☐	☐	☐	☐
16	Had difficulty holding a drink without spilling it?	☐	☐	☐	☐	☐
17	Felt depressed?	☐	☐	☐	☐	☐
18	Felt isolated and lonely?	☐	☐	☐	☐	☐
19	Felt weepy or tearful?	☐	☐	☐	☐	☐
20	Felt angry or bitter?	☐	☐	☐	☐	☐
21	Felt anxious?	☐	☐	☐	☐	☐
22	Felt worried about your future?	☐	☐	☐	☐	☐
23	Felt you had to conceal your Parkinson's from people?	☐	☐	☐	☐	☐
24	Avoided situations which involve eating or drinking in public?	☐	☐	☐	☐	☐
25	Felt embarrassed in public due to having Parkinson's disease?	☐	☐	☐	☐	☐
26	Felt worried by other people's reaction to you?	☐	☐	☐	☐	☐
27	Had problems with your close personal relationships?	☐	☐	☐	☐	☐
28	Lacked support in the ways you need from your spouse or partner?	☐	☐	☐	☐	☐
	If you do not have a spouse or partner tick here		☐			
29	Lacked support in the ways you need from your family or close friends?	☐	☐	☐	☐	☐

*Please check that you have ticked **one box for each question** before going on to the next page*

Due to having Parkinson's disease, how often <u>during the last month</u> have you....		***Please tick <u>one</u> box for each question***				
		Never	**Occasionally**	**Sometimes**	**Often**	**Always or cannot do at all**
30	Unexpectedly fallen asleep during the day?	☐	☐	☐	☐	☐
31	Had problems with your concentration, e.g. when reading or watching TV?	☐	☐	☐	☐	☐
32	Felt your memory was bad?	☐	☐	☐	☐	☐
33	Had distressing dreams or hallucinations?	☐	☐	☐	☐	☐
34	Had difficulty with your speech?	☐	☐	☐	☐	☐
35	Felt unable to communicate with people properly?	☐	☐	☐	☐	☐
36	Felt ignored by people?	☐	☐	☐	☐	☐
37	Had painful muscle cramps or spasms?	☐	☐	☐	☐	☐
38	Had aches and pains in your joints or body?	☐	☐	☐	☐	☐
39	Felt unpleasantly hot or cold?	☐	☐	☐	☐	☐

*Please check that you have ticked **one box for each question** before going on to the next page*

Thank you for completing the PDQ 39 questionnaire

EuroQoL EQ-5D

Appendix F

Please answer the questions by ticking one box in each group.

Please indicate which statement best describes your own health today.

Do not tick more than one box in each group.

1 Mobility

- I have no problems walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

2 Self care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

3 Usual activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

4 Pain / Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

5 Anxiety/ Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

Please continue overleaf

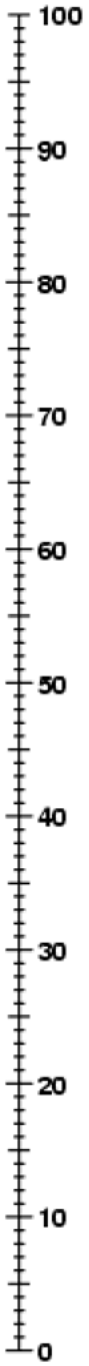
Your own health state today

To help people say how good or bad their health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you could imagine is marked by 0

We would like you to indicate on the scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box to whichever point on the scale indicates how good or bad your current health state is.

Your own health state today

Best imaginable health state



Worst imaginable health state

Please complete the following

PD MED Trial Number

Patient Initials: .....

Date of Birth: ..... / ..... / .....

Date Completed: ..... / ..... / .....

Trial office use only

Date Sent: / /

Date Received: ..... / ..... / .....

Date Entered: ..... / ..... / .....

Baseline 6 month 1yr 2yr 3yr 4yr 5yr

(please circle as appropriate)

SF-36 Version 2

Baseline 6 month 1yr 2yr 3yr 4yr 5yr

(please circle as appropriate)

OVERALL HEALTH

The following questions ask for your views about your health and how you feel about life in general. If you are unsure about how to answer any question, try and think about your overall health and give the best answer you can. Do not spend too much time answering, as your immediate response is likely to be the most accurate.

Please be sure to answer each question

---

1. <u>In general</u>, would you say your health is:

(Please tick **one** box)

- Excellent ☐
- Very good ☐
- Good ☐
- Fair ☐
- Poor ☐

---

2. <u>Compared to 3 months ago</u>, how would you rate your health in general now?

(Please tick **one** box)

- Much better than 3 months ago ☐
- Somewhat better than 3 months ago ☐
- About the same ☐
- Somewhat worse now than 3 months ago ☐
- Much worse now than 3 months ago ☐

3. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

(Please tick **one** box on each line)	Yes, limited a lot	Yes, limited a little	No, not limited at all
a) **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
b) **Moderate activities**, such as moving a table, pushing a vacuum, bowling or playing golf	☐	☐	☐
c) Lifting or carrying groceries	☐	☐	☐
d) Climbing **several** flights of stairs	☐	☐	☐
e) Climbing **one** flight of stairs	☐	☐	☐
f) Bending, kneeling or stooping	☐	☐	☐
g) Walking **more than a mile**	☐	☐	☐
h) Walking **half a mile**	☐	☐	☐
i) Walking **100 yards**	☐	☐	☐
j) Bathing and dressing yourself	☐	☐	☐

---

4. During the <u>past 2 weeks</u>, how much time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

(Please tick **one** box on each line)		**All of the time**	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**
a)	Cut down on the *amount of time* you spent on work or other activities	☐	☐	☐	☐	☐
b)	Accomplished less than you would like	☐	☐	☐	☐	☐
c)	Were limited in the kind of work or other activities	☐	☐	☐	☐	☐
d)	Had difficulty performing the work or other activities (e.g. it took more effort)	☐	☐	☐	☐	☐

5. During the <u>past 2 weeks</u>, how much time have you had any of the following problems with your work or other regular daily activities *as a result of any emotional problems* (such as feeling depressed or anxious)?

(Please tick **one** box on each line)

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a)	Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b)	**Accomplished less** than you would like	☐	☐	☐	☐	☐
c)	Didn't do work or other activities as **carefully** as usual	☐	☐	☐	☐	☐

---

6. During the <u>past 2 weeks</u>, to what extent have your physical health or emotional problems interfered with your normal social activities with family, neighbours or groups?

(Please tick **one** box)

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

---

7. How much bodily pain have you had during the <u>past 2 weeks</u> ?

(Please tick **one** box)

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very Severe ☐

8. During the <u>past 2 weeks</u>, how much did pain interfere with your normal work (including both outside the home and housework)?

(Please tick **one** box)

Not at all	☐
Slightly	☐
Moderately	☐
Quite a bit	☐
Extremely	☐

---

9. These questions are about how you feel and how things have been with you during the <u>past 2 weeks</u>. For each question please give one answer that comes closest to the way you have been feeling.

How much time during the <u>last 2 weeks</u>:	**All of the time**	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
a) Did you feel full of life?	☐	☐	☐	☐	☐	☐
b) Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
c) Have you felt so down in the dumps that nothing would	☐	☐	☐	☐	☐	☐
d) Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
e) Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
f) Have you felt downhearted and low?	☐	☐	☐	☐	☐	☐
g) Did you feel worn out?	☐	☐	☐	☐	☐	☐
h) Have you been a happy person?	☐	☐	☐	☐	☐	☐
i) Did you feel tired?	☐	☐	☐	☐	☐	☐

10. During the <u>past 2 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives etc.)?

(Please tick **one** box)

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

---

11. How TRUE or FALSE is each of the following statements for you?

(Please tick **one** box on each line)		**Definitely true**	**Mostly true**	**Not sure**	**Mostly false**	**Definitely false**
a)	I seem to get ill more easily than other people	☐	☐	☐	☐	☐
b)	I am as healthy as anybody I know	☐	☐	☐	☐	☐
c)	I expect my health to get worse	☐	☐	☐	☐	☐
d)	My health is excellent	☐	☐	☐	☐	☐

---

12. During the last 12 months, how many hours on average per day have you spent caring for the person suffering from Parkinson's disease?

Hours per day

_____

If you did not have to spend this time caring, what would you otherwise have done with these hours? (please tick all those relevant activities and the number of hours which would have been spent on each).

Paid employment hours ☐ _____ hours

Leisure activities such as gardening/reading/relaxing hours ☐ _____ hours

Other (e.g. shopping, housework) hours ☐ _____ hours

If other, please specify _____

Completed by: _____ Date ___/___/___

RANDOMISATION NOTEPAD

Prepare for the randomisation questions by filling in sections A, B, C, D, E and F on this pad before telephoning the toll free randomisation service on 0800 953 0274 for immediate randomisation, or fax form to 0121 415 9135 for allocation by next working day.

PART A: IDENTIFYING DETAILS

Randomising Consultant…….. Hospital Name……..

Patient's Full name:…… Gender: Male ☐ Female ☐ Title: Mr/Mrs/Ms/Miss/Other……..

PART B: ELIGIBILITY

Is the patient demented? No ☐ Yes ■

Is the patient able to complete the questionnaire? No ■ Yes ☐ *(with help, if necessary)*

Has the patient given written informed consent? No ■ Yes ☐

PART C: PATIENT'S MEDICAL DETAILS

Date of initial diagnosis of PD (month/year) …../….. Yoehn & Yahr Stage ……. (see protocol, appendix A)

Stage of PD Early ☐ Later ☐

If Early: Any previous PD therapy? No ☐ <1 month ☐ 1 – 3 months ☐ 3 – 6 months ☐ > 6 months ■

If previous therapy, please specify……..

If later: Patient previously entered in PD MED trial? No ☐ Yes ☐ if yes, PD MED trial number…….

Current therapy: DA: Yes ☐ No ☐ MAOBI: Yes ☐ No ☐ COMTI: Yes ☐ No ☐

PART D: TREATMENT DETAILS

Willing to randomise to MAOBI: No ☐ Yes ☐ Willing to randomise to LD alone (early PD only): No ☐ Yes ☐

If allocated DA, which DA will be prescribed?.....

If allocated MAOBI, which MAOBI will be prescribed?.....

If allocated COMTI, which COMTI will be prescribed?..... (later PD only)

PART E: QUESTIONNAIRES

Has the patient completed? PDQ39: No ■ Yes ☐ Euroqol EQ-5D: No ■ Yes ☐

Has the MMSE been administrated? No ■ Yes ☐

PART F: CARER DETAILS

Does the patient have a regular carer? No ☐ Yes ☐ If yes, name of principal carer…….

Has the carer completed the SF-36? No ☐ Yes ☐ Relationship…….

If No, reason (eg no carer, carer declined to take part)……

PART G: TREATMENT ALLOCATION from RANDOMISATION SERVICE 0800 953 0274

Early PD LD only ☐ Dopamine agonist ☐ MAOB inhibitor ☐

Later PD Dopamine agonist ☐ MAOB inhibitor ☐ COMT inhibitor ☐

PD MED trial number:……

Contact person…….. Fax No: …… Telephone No:……..

(for queries or fax allocations)

Please file the top copy of this form in the patient notes, and return the bottom copy along with the questionnaires listed in Part E (and F if applicable) and consent form within one week of trial entry to the PD MED Trial Office. A Freepost envelope is supplied for return to The University of Birmingham, Birmingham Clinical Trials Unit, Division of Medical Sciences, Robert Aitken Institute, **FREEPOST RRKR-JUZR-HZHG**, Birmingham B15 2TT

Appendix I

GP LETTER

Doctor
Practice
Street
City
Postcode

NAME DATE RANDOMISED

DATE OF BIRTH PD MED NUMBER

HOSPITAL NUMBER

Dear Dr *gp*

Your patient, named above, has agreed to take part in PD MED, a randomised assessment of the relative cost effectiveness of the different classes of drugs used for Parkinson's disease (PD) in which we, and many other centres in the UK, are participating. PD MED is organised by the University of Birmingham Clinical Trials Unit and funded by the Health Technology Assessment (HTA) Programme of the NHS. PD MED is a large, simple, "real-life" trial that aims to determine reliably which class of drugs provides the most clinically and cost-effective control in both early and later PD. The trial is designed to fit in with routine practice as far as possible and to impose minimal additional workload: clinicians can use the specific drug within the allocated class that they prefer.

Patients with early PD are randomised between dopamine agonist (± levodopa) versus monoamine oxidase type B inhibitor (MAOBI) (± levodopa) and levodopa alone. Those with later PD are randomised between DA versus MAOBI versus catechol-O-methyltransferase inhibitor (COMTI).

The above patient has been entered into the *early/late* randomisation and has been allocated:

Class (with *drug* chosen as the specific drug).

When you supply repeat prescriptions for this patient, would you please continue to prescribe *drug* unless advised otherwise by their consultant.

The principal investigator for the trial is Dr *participant.* The trial has been approved by the West Midlands Multi-Centre Research Ethics Committee and *regional* Local Research Ethics Committee.

If you require any further information about the study, it can be obtained from me or from the PD MED Trial Office (see address below). Please file this letter in the patient's notes. I would appreciate being notified if he/she is no longer one of your patients.

Yours sincerely

Consultant
Department of *Neurology/Geriatrics*, *hospital*.

PD MED Trial Office, The University of Birmingham Clinical Trials Unit,
FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, Vincent Drive, Edgbaston, Birmingham, B15 2TT
Tel: 0121 415 9127/9128/9129 Fax: 0121 415 9135 E-mail: pd-trials@bham.ac.uk

RESOURCE USAGE

Your use of health and social services due to Parkinson's Disease

We would like to know how much use you have made of the health and social services **over the last 12 months** because of your Parkinson's disease. If you are not exactly sure,

Please answer every question, even if the answer is None ["0"]

1. Over the last 12 months, how many times have you:

Been seen by your GP ?	☐
Been seen by a practice nurse ?	☐
Been seen by a Parkinson's disease nurse?	☐
Been seen by a health visitor ?	☐
Been seen by a social worker?	☐
Been seen by a physiotherapist?	☐
Been seen by a occupational therapist?	☐
Been seen by a speech/language therapist?	☐
Visited a day hospital?	☐
Visited a hospital out-patient clinic?	☐

2.If you have had any overnight hospital stays <u>because of your Parkinson's disease</u> in the last 12 months, please state the total number of nights , for respite or treatment.

	Total number of nights	Please give the reasons:
Respite Care	☐	_____
Treatment	☐	_____

3. Over the last 12 months, have you used or received the following services?

Home care/home help	No	☐	Yes	☐	If yes, how many times per week?	☐
Meals on wheels	No	☐	Yes	☐	If yes, how many times per week?	☐
Day centre	No	☐	Yes	☐	If yes, how many times per week?	☐
Luncheon Club	No	☐	Yes	☐	If yes, how many times per week?	☐
Sitting Service	No	☐	Yes	☐	If yes, how many times per week?	☐
Night Care	No	☐	Yes	☐	If yes, how many times per week?	☐

4. Over the last 12 months, have you consulted a private practitioner such as an Acupuncturist, Aromatherapist or Reflexologist as a result of your Parkinson's disease?

No ☐ Yes ☐ If Yes, please state how many times: ☐

5. Are you currently, or in the last 12 months have you been, in paid employment?

Yes ☐ Go to 5a No ☐ Go to 5b

5a **If Yes, due to your Parkinson's disease** have you had to reduce the number of hours per week you work over the last 12 months? (*please tick only one*).

☐ No, I work the same hours. Please state how many hours this is ☐

☐ Yes, I have had to reduce my hours by ☐ hours per week.

☐ Yes, I have had to stop work completely.

5b **If you are not employed**: in the last 12 months have you had to reduce the number of hours per week you spend carrying out your normal daily activities, **due to your Parkinson's disease**,?

☐ No ☐ Yes I have had to reduce my hours by ☐ hours per week.

6. Do you have regular carers who are family members or friends? No ☐ Yes ☐

If Yes, please state how many family/friends carers you have in total ☐

Please state relationship of main carer: _____

In the last 12 months, please state how many hours on average each carer has spent caring for you per week:

Main carer: ☐ hours per week Other carer: ☐ hours per week

Other carer: ☐ hours per week Other carer: ☐ hours per week

7. Are you currently receiving benefits? No ☐ Yes ☐

If Yes, what level have you been receiving in the last 12 months?

Low ☐ Medium ☐ High ☐

8. If you would like to tell us about any costs incurred because of your Parkinson's disease over the last 12 months, please write them here.

_____

_____

_____

_____

Please return this form, with the others, in the FREEPOST envelope provided.

ANNUAL FOLLOW-UP FORM
EARLY DISEASE

Appendix K

Part A: Identification Details

To be completed by patient's hospital doctors

Patient's initials: ☐ ☐ PD MED Trial No E ☐ ☐ ☐ ☐ ☐

Date of birth: / / Hospital number: _____

Hospital _____

Is the diagnosis still idiopathic Parkinson's Disease? No ☐ Yes ☐

If not, what is the most likely diagnosis? _____

N.B. The patient will still be followed up within PD MED

Part B: Current Disease Status

Hoehn and Yahr Stages

Stage 1.0 Unilateral involvement only
Stage 1.5 Unilateral and axial involvement
Stage 2.0 Bilateral involvement without impairment of balance
Stage 2.5 Mild bilateral involvement with recovery on retropulsion (pull) test
Stage 3.0 Mild to moderate bilateral involvement, some postural instability but physically independent
Stage 4.0 Severe disability, still able to walk and to stand unassisted
Stage 5.0 Wheelchair bound or bedridden unless aided.

Date of assessment: / /

Patient's current Hoehn & Yahr stage: ☐

Please ask the patient if they have suffered (a) any involuntary movements, other than tremor, and demonstrate typical athetoid dyskinesia to them or (b) wearing off of one dose of medication before the next is due. If the reply is affirmative, or if you or the carer have witnessed these phenomena, please record the findings below.

Has the patient developed motor complications? No ☐ Yes ☐

What type of motor complications have developed?

Dyskinesia No ☐ Yes ☐ **If Yes**, date started (mo/yr): /

Fluctuations No ☐ Yes ☐ **If Yes**, date started (mo/yr): /

Has the patient developed dementia? No ☐ Yes ☐ **If Yes**, date of diagnosis (mo/yr) /
(as defined by the clinician's usual criteria)

Has the patient been institutionalised? No ☐ Yes ☐ **If Yes**, date admitted (mo/yr) /

Type of home: Nursing ☐ Residential ☐

Has the patient died? No ☐ Yes ☐ **If Yes**, date of death: / /

Cause of death: _____

If the patient has died, please give details of therapy prior to death in Part C.

Part C: Current Therapy

Please give details of the patient's current drug therapy for PD including treatment related to PD
(e.g. anti-depressants, anti-psychotic):

Example of patients current drug therapy

Drug	Dose	Total daily dose (mg)	Date Started
Sinemet Plus	100mg x 5 daily	500	5/10/00
Bromocriptine	10mg + 5mg + 10mg	25	25/5/99

Drug	**Dose**	**Total daily dose (mg)**	**Date Started**
			/ /
			/ /
			/ /
			/ /

If the medication has changed since the last follow-up, **please record the changes and reasons on the reverse side to this form**

Assessor: _____ Signature: _____ Date: / /

Please return this form to: **PD MED Trial Office, The University of Birmingham, Birmingham Clinical Trials Unit, Robert Aitken Institute, FREEPOST RRKR-JUZR-HZHG, Birmingham, B15 2TT**

Year of follow-up

1	2	3	4	5	

DRUG	**Date Started** approximate	**Date Stopped** approximate	**Reason stopped or changed** (please specify side effects)

If appropriate, please send a copy of GP letter

ANNUAL FOLLOW-UP FORM
LATER DISEASE

Part A: Identification Details

To be completed by patient's hospital doctors

Patient's initials: ☐ ☐ PD MED Trial No **A** ☐ ☐ ☐ ☐

Date of birth: / / Hospital number:

Hospital

Is the diagnosis still idiopathic Parkinson's Disease? No ☐ Yes ☐

If not, what is the most likely diagnosis?

N.B. The patient will still be followed up within PD MED

Part B: Current Disease Status

Date of assessment: / /

Patient's current Hoehn & Yahr stage: ☐

Hoehn and Yahr Stages
Stage 1.0 Unilateral involvement only
Stage 1.5 Unilateral and axial involvement
Stage 2.0 Bilateral involvement without impairment of balance
Stage 2.5 Mild bilateral involvement with recovery on retropulsion (pull) test
Stage 3.0 Mild to moderate bilateral involvement, some postural instability but physically independent
Stage 4.0 Severe disability, still able to walk and to stand unassisted
Stage 5.0 Wheelchair bound or bedridden unless aided.

Has the patient developed dementia? No ☐ Yes ☐ **If Yes**, date admitted (mo/yr) /
(as defined by clinician's usual criteria)

Has the patient been institutionalised? No ☐ Yes ☐ **If Yes**, date admitted (mo/yr) /

Type of home: Nursing ☐ Residential ☐

Has the patient died? No ☐ Yes ☐ **If Yes**, date of death: / /

Cause of death:

If the patient has died, please give details of therapy prior to death in Part C.

Part C: Current Therapy

Please give details of the patient's current drug therapy for PD including treatment related to PD (e.g. anti-depressants, anti-psychotic):

Example of patients current drug therapy

Drug	Dose	Total daily dose (mg)	Date Started
Sinemet Plus	100mg x 5 daily	500	5/10/01
Bromocriptine	10mg + 5mg + 10mg	25	25/5/01

Drug (including Apomorphine)	**Dose**	**Total daily dose (mg)**	**Date Started**
			/ /
			/ /
			/ /
			/ /

If the medication has changed since the last follow-up, **please record the changes and reasons on the reverse side to this form.**

Has the patient been considered for PD related surgery? No ☐ Yes ☐

If Yes, date considered for surgery (mon/yr) /

Reason for surgery:

Assessor: Signature: Date: / /

Please return this form to:

PD MED Trial Office, The University of Birmingham, Birmingham Clinical Trials Unit, Robert Aitken Institute, FREEPOST RRKR-JUZR-HZHG, Birmingham, B15 2TT

Please complete the following
PD MED Trial Number

Patient Initials: .....
Date of Birth: ..... / ..... / .....
Date Completed: ..... / ..... / .....

Trial office use only
Date Sent: ..... / ..... / .....
Date Received: ..... / ..... / .....
Date Entered: ..... / ..... / .....

Year of follow-up

1	2	3	4	5	

DRUG	**Date Started** approximate	**Date Stopped** approximate	**Reason stopped or changed** (please specify side effects)

If appropriate, please send a copy of GP letter

Side effects , drug changes and hospitalisation

Please complete the following
PD MED Trial Number

Patient Initials: .....
Date of Birth: ..... / ..... / .....
Date Completed: ..... / ..... / .....

Trial office use only
Date Sent: ..... / ..... / .....
Date Received: ..... / ..... / .....
Date Entered: ..... / ..... / .....

Side Effects

We would also like to know if you have had any side effects while taking your PD drugs since last completing a questionnaire and, if you have stopped taking any of them, the reasons for stopping.

Have you had any side effects? No ☐ Yes ☐

If Yes, please give details below ?

Changes to drugs

Have you stopped taking (or changed) any of your PD drugs since completing the last questionnaire?

No ☐ Yes ☐

If Yes, please give details below ?

Hospitalisation

Have you had to stay in hospital, a residential home or a nursing home for any reason since last completing a questionnaire?

No ☐ Yes, Hospital ☐ Yes, Nursing Home ☐ Yes, Residential Home ☐

If yes, please give details (continue overleaf if needed):

Where stayed	Reason	No. of days/Approximate date

Questionnaires completed: …./……/……. Signature:----------

SERIOUS ADVERSE EVENT FORM

Please report any **serious, unexpected** adverse events***** believed to be due to the treatments given as part of the PD MED trial by completing this form and returning as soon as possible to the PD MED Trial Office

Patient's full name: _____

Date of birth: / / PD MED Trial No ☐☐☐☐☐

Hospital Number

Hospital _____

Responsible doctor: _____

Date event started: / / Date event ceased: / /

Outcome: Fatal ☐ Recovered ☐ Continuing ☐

Details of adverse event (please attach copies of relevant reports): _____

Did the event require or prolong hospitalisation? No ☐ Yes ☐ No.of days: ☐

Please give reasons why if you consider the event to be treatment-related: _____

Name of person reporting:
(please PRINT) _____

Telephone Number _____

Signed: _____ Date / /

Please return this form, as soon as possible, (with copies of any relevant reports) to:

PD MED Trial Office, The University of Birmingham, Birmingham Clinical Trials Unit, Robert Aitken Institute, FREEPOST RRKR-JUZR-HZHG, Birmingham, B15 2TT
or fax to 0121 415 9135

*****For the purposes of this study, **"serious"** adverse events are those which are fatal, life-threatening, disabling or require hospitalisation. **"Unexpected"** adverse events are defined as those that would not be expected among elderly patients given anti-parkinsonian medication (which has certain expected side-effects) for Parkinson's disease (which has expected symptoms).

Appendix N

AVAILABILITY AND DOSAGE OF DRUGS

Drug / Class	Tradename	Company	Average Dose (stable)
Co-Beneldopa / LD	Madopar	Roche	750mg (6 x125mg)
Co-Careldopa / LD	Sinemet	BMS	750mg (6 x 125mg)
Bromocriptine / DA	Parlodel	Novartis / Non-proprietary	25mg (10 x 2.5mg)
Cabergoline / DA	Cabaser	Pharmacia	4mg (1 x 4mg)
Pergolide / DA	Celance	Lilly	3mg (3 x 1mg)
Ropinirole / DA	Requip	SKB	15mg (3 x 5mg)
Pramipexole / DA	Mirapex	Pharmacia	3n (3 x 1mg)
Selegiline / MAOBI	Eldepryl	Orion / Non-proprietary	10mg (1 x l0mg) (2 x 5mg)
Selegiline / MAOBI (Sub-lingual)	Zelapar	Elan	1.25mg (1 x 1.25mg)
Entacapone / COMTI	Comtess	Orion	1000mg (5 x 200mg)

DRUG TITRATION REGIMENS (DOPAMINE AGONISTS)

WEEK	BROMOCRIPTINE	CABERGOLINE	ROPINIROLE	PRAMIPEXOLE
Week 1	1-1.25 mg at night	1 mg once daily	0.25 mg tds	0.125 mg tds
Week 2	2-2.5 mg at night	2 mg once daily~	0.5 mg tds	0.25 mg tds
Week 3	2.5 mg bd	3 mg once daily	0.75 mg tds	0.5 mg tds
Week 4	2.5 mg tds ⬟	4 mg once daily	1 mg tds	0.75 mg tds
Week 5	N/A	5 mg once daily	2 + 1 + 1 mg daily	1 mg tds
Week 6	N/A	6 mg once daily	2 + 2 + 1 mg daily	1.25 mg tds
Week 7	N/A	N/A	2 mg tds	1.5mg tds
Week 8	N/A	N/A	4 + 2 + 2 mg daily	N/A
Week 9	N/A	N/A	4 + 4 + 2 mg daily	N/A
Week 10	N/A	N/A	N/A	N/A

⬟Then every 3-10 days: additional 2.5 mg to usual range of 10-40 mgs.

~Therapeutic dose 2-6 mg/day

Regimes are derived from Summary of Product Characteristics.

Appendix N

DRUG TITRATION REGIMENS (DOPAMINE AGONISTS)

DAYS	PERGOLIDE
Days 1 and 2	50 µg (microgrammes) once at night
Days 3 and 4	50 µg tds
Days 5 and 6	50 + 100 + 100 µg daily
Days 7 and 8	100 + 100 + 150 µg daily
Days 9 and 10	150 µg tds
Days 11 and 12	200 µg tds
Days 13 and 14	250 µg tds
Days 15, 16 and 17	500 + 250 + 250 µg daily
Days 18, 19 and 20	500 + 500 + 250 µg daily
Days 21, 22 and 23	500 µg tds
Days 24, 25 and 26	750 + 500 + 500 µg daily
Days 27, 28 and 29	750 + 750 + 500 µg daily
Days 30, 31 and 32	750 µg tds
Days 33, 34 and 35	1000 + 750 + 750 µg daily
Days 36, 37 and 38	1000 + 1000 + 750 µg daily
Days 39, 40 and 41	1000 µg tds
Days 42, 43 and 44	1250 + 1000 + 1000 µg daily
Days 45, 46 and 47	1250 + 1250 + 1000 µg daily
Days 48, 49 and 50	1250 µg tds
Days 51, 52 and 53	1500 + 1250 + 1250 µg daily
Days 54, 55 and 56	1500 + 1500 + 1250 µg daily
Days 57, 58 and 59	1500 µg tds
Days 60, 61 and 62	1750 + 1500 + 1500 µg daily
Days 63, 64 and 65	1750 + 1750 + 1500 µg daily
Day 66 onwards	1750 µg tds

µg = microgramme = mcg

TOXICITY OF DRUGS

Drug	Minor Side Effects	Major Side Effects	Interactions
Levodopa	Drowsiness Dizziness Loss of appetite Stomach upset Nausea Darkening of the urine or sweat	Vomiting Difficulty swallowing Difficulty urinating Uncontrollable movements Chest pain Irregular heartbeat Skin rash Mood or mental changes	Some monoamine oxidase inhibitors Vitamin B6 (pyridoxine) and other vitamin products that contain pyridoxine
Selegiline	Dizziness Loss of appetite Stomach upset Nausea Heartburn Dry mouth Increased sensitivity to sunlight	Severe headache Chest pain Difficulty in breathing Difficulty in urination Uncontrollable movements/ clumsiness Irregular heartbeat Confusion Hallucinations	Some monoamine oxidase inhibitors Drugs used for depression Narcotic pain relievers Certain sympathomimetics found in over-the-counter cold remedies and asthma inhalers Diabetic drugs Fenfluramine/dexfenfluramine Watch intake of foods containing tyramine
Bromocriptine	Drowsiness Headache Stomach cramps Nausea/vomiting Indigestion Constipation Diarrhoea Fatigue Light-headedness Insomnia Nasal congestion	Blood in vomit Confusion Fainting Depression Irregular pulse Shortness of breath Rash Tingling of hands or feet Involuntary movements Nightmares Vision problems	Oral contraceptives Levodopa Medication for high blood pressure Medication for migraine headaches Medications for depression
Cabergoline	Drowsiness Dizziness Nausea or vomiting Unusual weakness or fatigue Constipation Headache Tingling or numbness sensation	Fainting Leg or foot swelling Breast pain or menstrual problems Vision problems Mental/mood changes	Medications for high blood pressure Drugs used for psychosis and anxiety Sedatives Sleep medication Anti-seizure drugs Narcotic pain relievers Certain antihistamines e.g. diphenhydramine, Certain muscle relaxants Metoclopramide
Ropinirole	Drowsiness Dizziness Stomach upset Nausea Constipation Trouble sleeping Unusual weakness Headache Dry mouth	Difficulty in moving, walking or breathing Restlessness Muscle pain and/or severe muscle stiffness Leg or foot swelling Irregular heartbeat Chest pain Fainting Confusion Hallucinations Vision problems	Other drugs for Parkinson's disease Drugs used for psychosis, anxiety or depression Tranquillisers Anti-seizure drugs Narcotic pain relievers Sleep medication Certain antihistamines e.g. diphenhydramine, ciprofloxacin Certain muscle relaxants Metoclopramide Cimetidine

TOXICITY OF DRUGS (continued)

Drug	Minor Side Effects	Major Side Effects	Interactions
Pramipexole	Drowsiness Dizziness Stomach upset Nausea Constipation Trouble sleeping Unusual weakness Headache Dry mouth	Difficulty in moving, walking or breathing Restlessness/twitching Muscle pain and/or severe muscle stiffness Leg or foot swelling Irregular heartbeat Chest pain Fainting Confusion Hallucinations Vision problems	Other drugs for Parkinson's disease Drugs used for psychosis, anxiety or depression Tranquillisers Anti-seizure drugs Narcotic pain relievers Sleep medication Certain antihistamines e.g. diphenhydramine Certain muscle relaxants Metoclopramide Cimetidine
Pergolide	Drowsiness Dizziness Loss of appetite Nausea Constipation Headache Dry mouth	Difficulty in moving, walking or breathing Restlessness Muscle pain and/or severe muscle stiffness Leg or foot swelling Irregular heartbeat Chest pain Fainting Fever Confusion Hallucinations Vision problems	Other drugs for Parkinson's disease Drugs used for psychosis, anxiety or depression Tranquillisers Anti-seizure drugs Narcotic pain relievers Sleep medication Certain antihistamines e.g. diphenhydramine, ciprofloxacin Certain muscle relaxants Metoclopramide Cimetidine
Entacapone	Diarrhea Nausea Drowsiness Dizziness	Abdominal pain Dyskinesia Urine discolouration Hallucinations Orthostatic hypotension Hepatic function impairment Renal function impairment	Monoamine oxidase inhibitors

ICECAP-O

ABOUT YOUR QUALITY OF LIFE: By placing a tick (✓) in ONE box in EACH group below, please indicate which statement best describes your quality of life at the moment.

I can have all of the love and friendship that I want	
I can have a lot of the love and friendship that I want	
I can have a little of the love and friendship that I want	
I cannot have any of the love and friendship that I want	

2. Thinking about the future	
I can think about the future without any concern	
I can think about the future with only a little concern	
I can only think about the future with some concern	
I can only think about the future with a lot of concern	

3. Doing things that make you feel valued	
I am able to do all of the things that make me feel valued	
I am able to do many of the things that make me feel valued	
I am able to do a few of the things that make me feel valued	
I am unable to do any of the things that make me feel valued	

4. Enjoyment and pleasure	
I can have all of the enjoyment and pleasure that I want	
I can have a lot of the enjoyment and pleasure that I want	
I can have a little of the enjoyment and pleasure that I want	
I cannot have any of the enjoyment and pleasure that I want	

5. Independence	
I am able to be completely independent	
I am able to be independent in many things	
I am able to be independent in a few things	
I am unable to be at all independent	

Tick one box only in each section

Carer Experience Scale

PLEASE TICK ONE BOX FOR EACH GROUP to indicate which statement best describes your current caring situation.

1.Activities outside caring ***(Socialising, physical activity and spending time on hobbies, leisure or study)*** ☐1

You can do most of the other things you want to do outside caring …… ☐2
You can do some of the other things you want to do outside caring ……
You can do few of the other things you want to do outside caring …….. ☐3

2. Support from family and friends **(*Personal help in caring and/or emotional support from family, friends, neighbours or work colleagues)*** ☐1

You get a lot of support from family and friends …….. ☐2
You get some support from family and friends ……
You get little support from family and friends ……... ☐3

3. Assistance from organisations and the Government ***(Help from public, private or voluntary groups in terms of benefits, respite and practical information)*** ☐1

You get a lot of assistance from organisations and the Government …….. ☐2
You get some assistance from organisations and the Government ……
You get little assistance from organisations and the Government ……... ☐3

4. Fulfilment from caring ***(Positive feelings from providing care, which may come from: making the person you care for happy, maintaining their dignity, being appreciated, fulfilling your responsibility, gaining new skills or contributing to the care of the person you look after)*** ☐1

You mostly find caring fulfilling ……... ☐2
You sometimes find caring fulfilling ……
You rarely find caring fulfilling …… ☐3

5. Control over the caring ***(Your ability to influence the overall care of the person you look after)*** ☐1

You are in control of most aspects of the caring …… ☐2
You are in control of some aspects of the caring ……
You are in control of few aspects of the caring …… ☐3

6. Getting on with the person you care for ***(Being able to talk with the person you look after, and discuss things without arguing)*** ☐1

You mostly get on with the person you care for …….. ☐2
You sometimes get on with the person you care for ……..
You rarely get on with the person you care for …… ☐3

Appendix R

Lost To Follow UP

Dear <Title> <Surname>

I'm writing from the PD MED study office at the University of Birmingham. You very kindly agreed to take part in this Department of Health study, which aims to find out which of several possible treatments gives the best overall quality of life, with the fewest undesirable side effects, for people with Parkinson's disease. A strength of PD MED is that it is patients not doctors who say how their treatment affects their quality of life. But, we notice that you haven't completed the last two questionnaires that we sent you and would like to find out whether you received them or if there is any problem that makes completing questionnaires difficult for you. For the PD MED trial to provide reliable results that will help improve treatment of Parkinson's disease, it is very important that we know if patients are too ill to complete forms and so, if this applies to you, any information that you can provide us about your current health would be very helpful.

Could you please tick the boxes below that apply to you:	**Yes**	**No**
1. I can complete PD MED questionnaires if you send them to me	☐	☐
2. I could complete a short version of the questionnaire (just 8 questions)	☐	☐
3. Could you telephone me to ask the PD MED questions about my health Telephone number:_____	☐	☐
4. A spouse/ relative/ friend can complete PD MED questionnaires for me Name:_____ Telephone:_____	☐	☐
5. Could you ask one of the nurses to help me complete the questions	☐	☐
6. I won't be able to complete any more forms	☐	☐

If not, it would help if you could tell us why:_____

_____

_____

Thank you for your help.

Please return the form in the enclosed stamped addressed envelope

Dr Caroline Rick

PD MED Study Coordinator