

**ADHERENCE THERAPY FOR PEOPLE WITH
PARKINSON'S DISEASE**

THESIS APPENDICES

By

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Thesis submitted in fulfilment of the requirements
for the degree of Doctor of Philosophy
Norwich Medical School
Faculty of Medicine and Health Sciences
University of East Anglia

September 2013

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Appendix 1: Systematic Review Search Strings

Medline (Ovid)

1. exp Parkinsonian Disorders/
2. exp Patient Compliance/
3. Medication Adherence/
4. Treatment Refusal/
5. non\$adherence.mp.
6. non\$compliance.mp
7. (influencing adj3 factors).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
8. (caregiver adj3 compliance).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
9. Caregivers/
10. sub\$optimal.mp.
11. (drug adj3 adherence).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
12. (therapy adj3 adherence).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
13. (therapy adj3 compliance).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
14. exp "denial (psychology)"/
15. (drug adj3 compliance).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
16. Therapeutics.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
17. adherence.mp.
18. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 1 and 18

AMED

1. exp Patient Compliance/
2. Treatment Refusal/
3. non\$adherence.mp.
4. non\$compliance.mp.
5. (influencing adj3 factors).mp. [mp=abstract, heading words, title]
6. (caregiver adj3 compliance).mp. [mp=abstract, heading words, title]
7. Caregivers/
8. sub\$optimal.mp
9. (drug adj3 adherence).mp. [mp=abstract, heading words, title]
10. (therapy adj3 adherence).mp. [mp=abstract, heading words, title]
11. (therapy adj3 compliance).mp. [mp=abstract, heading words, title]
12. (drug adj3 compliance).mp. [mp=abstract, heading words, title]
13. Therapeutics.mp. [mp=abstract, heading words, title]
14. adherence.mp.
15. parkinson disease/
16. parkinsonism.mp.
17. parkinsonian.mp.
18. exp patient compliance/
19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 18
20. 15 or 16 or 17
21. 19 and 20

PsychINFO

1. Treatment Refusal/
2. non\$adherence.mp.
3. non\$compliance.mp.
4. (influencing adj3 factors).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. (caregiver adj3 compliance).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
6. Caregivers/
7. sub\$optimal.mp
8. (drug adj3 adherence).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
9. (therapy adj3 adherence).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
10. (therapy adj3 compliance).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
11. (drug adj3 compliance).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
12. Therapeutics.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
13. adherence.mp.
14. exp parkinson's disease/
15. exp treatment compliance/
16. treatment compliance/ or exp client attitudes/ or exp treatment barriers/ or exp treatment dropouts/ or exp treatment duration/ or exp treatment refusal/ or exp treatment withholding/

17. exp denial/ or exp defense mechanisms/

18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 15 or 16
or 17

19. 14 and 18

Embase

1. exp Parkinsonian Disorders/
2. exp Patient Compliance/
3. Medication Adherence/
4. Treatment Refusal/
5. non\$adherence.mp.
6. non\$compliance.mp.
7. (influencing adj3 factors).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
8. (caregiver adj3 compliance).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
9. Caregivers/
10. sub\$optimal.mp.
11. (drug adj3 adherence).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
12. (therapy adj3 adherence).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
13. (therapy adj3 compliance).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
14. exp "denial (psychology)"/
15. (drug adj3 compliance).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
16. Therapeutics.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
17. adherence.mp.
18. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 1 and 18

Appendix 2: Data Extraction for Included Studies

Study Design/ Aim	<ul style="list-style-type: none"> - Case-control study - Identify predisposing factors to DDS.
Participants	<ul style="list-style-type: none"> - 125 PD patients. n=25 with DDS, n=100 PD without DDS. - Outpatients attending PD clinic were assessed for DDS. - Included in a larger questionnaire-based study of personality in PD. - Participants identified following structured interview using clinical criteria for DDS. - Additional eligible patients were identified from notes and approached. - 25 none PD control (10 randomly recruited, 15 related to study PD patients) - Exclusion criteria: MMSE <26. - Mean age, DDS 43 yrs, without DDS 56 yrs - Disease duration, DDS 13 yrs, without DDS 9.5 yrs - MMSE 29, both groups - GDS, DDS 19, without DDS 10 - Alcohol intake, DDS 9.5, without DDS 3.0
Measurement Tools/ Outcomes	<ul style="list-style-type: none"> - Unified Parkinson's Disease Rating Scale (UPDRS) part 2 - Sensation Seeking Scale (SSS) - short version - Novelty Seeking from the Temperament and Character Inventory (TCI)
Statistical Analysis	<ul style="list-style-type: none"> - Behaviour Inhibition, behaviour Activation scales (BIS/BAS) - Geriatric Depression scale (GDS).
Results	<ul style="list-style-type: none"> - Logistic regression - Patients with DDS compared to those without DDS had: <ul style="list-style-type: none"> o a significantly younger age of PD onset o greater past experimental drug use o more depressive symptoms o scored higher on impulsive sensation seeking (ISS) o Higher alcohol intake. - Factors leading to DDS: <ul style="list-style-type: none"> o Novelty Seeking o Depression o Alcohol intake o Age of PD onset

Study Design/ Aim	<ul style="list-style-type: none"> - Cross-sectional Survey (over 3 months), single centre - A comprehensive examination of medication intake and characteristics of patients according to medication intake
Participants	<ul style="list-style-type: none"> - n=68 PD patients approached; n=6 declined, n=8 dropped out. - 54 PD outpatients selected by randomisation of two-thirds of the caseload from two consultant lists in a movement disorder team. - Inclusion criteria: patients fulfilling UK Brain Bank Criteria; prescribed at least one antiparkinsonian medication. - Exclusion criteria: Patients on monotherapy with Selegiline or Amantadine; patients unable to manipulate the MEMS caps. - Mean age, 61.9 - Male, 56% - Hoehn and Yahr score, 2.3 - Schwab & England, 79 - Mini Mental State Examination, 28 - Geriatric Depression Scale, 10.4
Measurement Tools/ Outcomes	<ul style="list-style-type: none"> - Antiparkinsonian drugs dispensed into Medication Electronic Measuring Devices (MEMS). - At three months, MEMS devices collected. - Patient perceived involvement in therapy management and satisfaction with movement disorders healthcare services were monitored.
Statistical Analysis	<ul style="list-style-type: none"> - Correlation between dose compliance, daily compliance, time interval compliance and other variables examined using linear regression.
Results	<ul style="list-style-type: none"> - 11 (20%) had average total compliance below 80% (i.e. underusers) - Linear regression revealed: <ul style="list-style-type: none"> o Younger age associated with poor adherence, o Depression associated with poor total compliance, o Poor Quality of Life associated with poor total compliance, o More tablets per day

Study Design/ Aim	<ul style="list-style-type: none"> - Cross-sectional Survey, multicentre in Spain - only academic tertiary and secondary hospitals from the public health system. - Determine demographic, social and clinical factors that influence therapy adherence in PD
Participants	<ul style="list-style-type: none"> - n=450 PD patients identified, n=32 missing data so excluded - 418 PD patients included - No sample size calculated due to lack of data - Inclusion criteria: clinical diagnosis of PD; prescribed any antiparkinsonian medication; physicians had to have know the patient for at least 1-yr - All participating Neurologists (n=169) identified 3 consecutive out-patients - Males, 61% - Married, 74% - Mean age, 70.2 yrs - Mean disease duration, 5.7 yrs - Hoehn and Yahr, stage 2 - Mean Schwab & England, 80 - Depression, 29.8% - Cognitive Impairment, 22.4%
Measurement Tools/ Outcomes	<ul style="list-style-type: none"> - Evaluation of symptom control (clinical vs no control) - Physician assessment of adherence based on a pre-defined question by the researchers - Morisky-Green 4-item scale (MMAS-4)
Statistical Analysis	<ul style="list-style-type: none"> - Evaluation of the patients' knowledge about PD with three simple questions
Results	<ul style="list-style-type: none"> - Bivariate & multivariate analysis - 39.6% were non adherent according to MMAS-4. 6.3% were non adherent according to physicians opinion. - Findings showed poor adherence in: <ul style="list-style-type: none"> o participants with low level knowledge of PD o poor clinical control o no spouse or life partner o low income o Psychiatric symptoms

Study Design/ Aim	<ul style="list-style-type: none"> - Cross-sectional Survey (over 1 month), single centre in the USA - To report on drug use in PD using MEMS
Participants	<ul style="list-style-type: none"> - n=40 PD patients identified from a medical centre. - No sample size calculated - Inclusion criteria: probable diagnosis of PD, taking at least 1 anti-parkinsonian medication three times daily or more. - Exclusion: MMSE<24; GDS>18; psychotropic or antidepressant use; history of delusions or hallucination; indication of assistance required to take medications; taking antiparkinsonian drugs on an as-needed basis. - Males (n=21) Females (n=18) - Age 68.3 - Level of education 13.3 yrs - Duration of disease 7.2 yrs - Number of drugs/day 5.2 - Number of doses/day 3.9 - Hoehn & Yahr 2.05 - GDS 4.8 - MMSE 28.6.
Measurement Tools/ Outcomes	<ul style="list-style-type: none"> - Adherence measured by MEMS caps for 1 month
Statistical Analysis	<ul style="list-style-type: none"> - Pearson's Correlation Coefficient - Chi squared test for independence - Fisher's exact test
Results	<ul style="list-style-type: none"> - Only 4 out of 39 (10%) completely adhered. MEMS recorded that 51.3% missed at least one dose per week and 20.55 missed three to four doses per week. - Only statistically significant factors predicting poor medication adherence: <ul style="list-style-type: none"> o Gender (female) o Level of education

Study Design/ Aim	<ul style="list-style-type: none">- A postal survey and one-to-one interviews- Data collected using both postal survey and one to one interviews.
Participants	<ul style="list-style-type: none">- n=339 returned postal questionnaire- Working age: females ≤59 and males ≤64- In paid employment at the time (164 males, 175 females)- n=24 people (11 males, 13females) were interviewed, mean age 51.6.- 4.9% reporting receiving their diagnosis within a year of initial symptoms.- 22.1% received a diagnosis within 2 years.- Other reported symptoms for many years prior to diagnosis.- n=103 (30.4%) 51 males and 52 females were in paid employment when completing the survey.
Measurement Tools/ Outcomes	
Statistical Analysis	N/A
Results	<ul style="list-style-type: none">- NDIST used for analysis of transcripts and open ended questionnaire items - Maintaining employment lead to the manipulation of drug regimens.

Study Design/ Aim	<ul style="list-style-type: none"> - Cohort study, 8 centres in 5 countries enrolled patients with PD. - To define the pattern of therapy adherence - To assess factors associated with non-adherence
Participants	<ul style="list-style-type: none"> - Inclusion: Taking Levodopa and/or dopamine receptor agonist and was expected to remain unchanged for 8/52. Able to use MEMS cap. - Exclusion: Taking therapy when needed; severe co-morbidity including dementia; planned hospital admission during study period. - n=112 PD patients. - <u>Satisfactory adherers:</u> - n=98, - 71% male, - age = 65, - PD duration = 7 yrs, - on Levodopa 81%, on dopamine agonist 74%, number of PD drugs = 2.2, number of administrations = 4.1, PD tablets per day = 7.2, - Hoehn and Yahr = 2.1, - GDS = 6, - PDQ-39 = 17, - UPDRS part 3= 19 - <u>Suboptimal adherers:</u> - n=14 - 65% male - age = 63 - PD duration = 10 yrs - On Levodopa 79%, on dopamine agonist 79%, number of PD drugs = 2.1, number of administrations = 5, PD tablets per day = 7.8 - Hoehn and Yahr = 2.5 - GDS = 10 - PDQ-39 = 26 - UPDRS part 3 = 29
Measurement Tools/ Outcomes	
Statistical Analysis	<ul style="list-style-type: none"> - Adherence measured by MEMS
Results	<ul style="list-style-type: none"> - Non-parametric assessed by Mann-Whitney U test. - Multiple linear regression - stepwise and forward - 12.5% took less than 80% of total prescribed medication. <ul style="list-style-type: none"> o Higher motor impairment assessed by UPDRS and PDQ-39 motor sub-score. o Timing adherence associated with total tablets, disease duration and age. o Complexity of regimens.

Study Design/ Aim	<ul style="list-style-type: none">- Exploratory qualitative study using semi-structured interviews- Explore how people with PD adhere to medication- Identify factors associated with medication non-adherence
Participants	<ul style="list-style-type: none">- 15 consecutive patients not in the advanced stages of PD and responsible for managing their own medication
Measurement Tools/ Outcomes	N/A
Statistical Analysis	Thematic analysis of interview transcripts
Results	<ul style="list-style-type: none">- Each participant demonstrated at least one type of non-adherence- Inadvertent minor non-adherence occurred because patients forgot to take tablets or muddled doses.- Minor deliberate deviations occurred when patients took occasional extra tablets or brought forward doses to achieve better symptom control, often to cater for situations that were anticipated as especially demanding.- Deliberate major non-adherence was very common and always related to over-use of medication.

Appendix 3: Cochrane Systematic Review Search Strings

Medline Ovid, AMED, CINAHL, PsychINFO and Embase

1. exp Patient Compliance/
2. exp Medication Adherence/
3. exp Patient Dropouts/
4. ((patient\$ or treatment\$ or medication or pharmaceutical or prescription) adj2 (compliance or noncompliance or complied or comply\$ or noncomply\$ or cooperate\$ or co-operate\$ or discontinu\$ or abstain\$ or stop\$ or adhere\$ or nonadhere\$ or abandon\$ or dropout\$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. 1 or 2 or 3 or 4
6. exp Parkinsonian Disorders/
7. (Parkinson's disease or Parkinson disease or PD, idiopathic Parkinson's disease).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8. 6 or 7
9. (education\$ adj2 (program\$ or intervention\$ or meeting\$ or session\$ or strategy\$ or workshop\$ or visit\$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
10. (pamphlet\$ or publication\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
11. (leaflet\$ or booklet\$ or poster or posters).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

12. ((written or oral or printed) adj information).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
13. (education\$ adj1 (method or material)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
14. exp Behavior Therapy/
15. ((cognitive or behaviour\$ or behavior\$) adj2 (intervention\$ or therapist\$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
16. exp interview/
17. (counseling or counselling).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
18. outreach.mp.
19. ((opinion or education\$ or influential) adj1 leader).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
20. facilitator.mp.
21. ((effect or impact or evaluat\$ or introduc\$ or compar\$) adj2 training program\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
22. exp Reminder Systems/

23. reminder.mp.
24. (recall adj2 system).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
25. (promoter adj2 promoting).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
26. exp Feedback/
27. (diary or diaries).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
28. ((followup or follow-up) adj appointment).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
29. tablet monitoring.mp.
30. (monitor\$ or surveillance).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
31. exp Self Care/
32. (medication adj2 manag\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
33. ((drug or dosage or dosing) adj regimen).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
34. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33

35. financial incentive\$.mp.
36. exp "Cost Sharing"/
37. (copayment or co payment).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
38. exp Hospital Charges/
39. 35 or 36 or 37 or 38
40. exp Physicians, Family/
41. exp Primary Health Care/
42. (primary adj2 (health or care or healthcare)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
43. ((health or healthcare or general) adj2 practitioner).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
44. exp Nurse Clinicians/
45. exp Nurses/
46. exp Nurse Practitioners/
47. (nurse adj (rehabilitation or clinician or practitioner)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
48. exp Pharmacists/

49. (case adj management).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

50. exp Outpatients/

51. (outpatient or ambulatory).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

52. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51

53. exp Home Care Services/

54. exp Day Care/

55. exp Office Visits/

56. exp Nursing Homes/

57. exp Aftercare/

58. community.mp.

59. exp Community Health Nursing/

60. domiciliary.mp.

61. (home adj1 treat).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

62. 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61

63. exp Program Evaluation/

64. (referral or consultation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

65. exp Drug Therapy/

66. exp Telephone/

67. (physician patient adj (interaction or relationship)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

68. exp Managed Care Programs/

69. 63 or 64 or 65 or 66 or 67 or 68

70. (progrma\$ adj2 (reduc\$ or increas\$ or decreas\$ or chang\$ or improv\$ or modify\$ or monitor\$ or care)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

71. (program\$ adj1 (health or care or intervention)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

72. ((effect or impact or evaluat\$ or introduc\$ or compar\$) adj2 treatment program\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

73. ((effect or impact or evaluat\$ or introduc\$ or compar\$) adj2 care program\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

74. ((effect or impact or evaluat\$ or introduc\$ or compar\$) adj2 screening program\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

75. ((effect or impact or evaluat\$ or introduc\$ or compar\$) adj2 prevent\$ program\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

76. (computer\$ adj2 (dosage or dosing or diagnosis or therapy or decision)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

77. ((introduc\$ or impact or effect\$ or implement\$ or computer\$) adj2 protocol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

78. ((effect or impact or introd\$) adj2 (legislation or regulations or policy)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

79. 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78

80. 34 or 39 or 52 or 62 or 69 or 79

81. exp Randomized Controlled Trial/

82. randomised controlled trial.mp.

83. RCT.mp.

84. exp Controlled Clinical Trial/

85. randomized.mp.

86. exp placebo effect/

87. exp Drug Therapy/

88. randomly.mp.

89. exp Clinical Trial/

90. groups.mp.

91. 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90

92. 5 and 8 and 80 and 91 (FINAL SEARCH COMBINATION)

Appendix 4: Criteria for Judging Risk of Bias

Type of Bias	Judgement	Criteria for Judgement
Random sequence generation	Low Risk	Describe a random component in the sequence generation process such as: <ul style="list-style-type: none"> • Referring to a random number table • Using a computer random number generator • Coin tossing • Shuffling cards or envelopes • Throwing dice • Drawing of lots
	High Risk	Describe a non-random component in the sequence generation process such as: <ul style="list-style-type: none"> • Sequence generated by odd or even date of birth • Sequence generated by some rule based on date (or day) of admission • Sequence generated by some rule based on hospital or clinic record number
	Unclear Risk	<ul style="list-style-type: none"> • Allocation by judgement of the clinician • Allocation by preference of the participant • Allocation based on the results of a laboratory test or a series of tests • Allocation by availability of the intervention <p>Insufficient information about the sequence generation process to permit judgement of ‘Low risk’ or ‘High risk’.</p>
Allocation Concealment	Low Risk	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: <ul style="list-style-type: none"> • Central allocation (including telephone, web-based and pharmacy-controlled randomization) • Sequentially numbered drug containers of identical appearance
	High Risk	<ul style="list-style-type: none"> • Sequentially numbered, opaque, sealed envelopes
	Unclear Risk	<p>Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:</p> <ul style="list-style-type: none"> • Using an open random allocation schedule (e.g. a list of random numbers) • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered) • Alternation or rotation • Date of birth • Case record number • Any other explicitly unconcealed procedure <p>Insufficient information to permit judgement of ‘Low risk’ or ‘High risk’. This is usually the case if the method of concealment is not described or not described in</p>

		sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
Blinding – participants & Personnel	Low Risk	Anyone of the following: <ul style="list-style-type: none"> No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High Risk	
	Unclear Risk	Any one of the following: <ul style="list-style-type: none"> No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding <p>Any one of the following:</p> <ul style="list-style-type: none"> Insufficient information to permit judgement of ‘Low risk’ or ‘High risk’ The study did not address this outcome
Blinding of outcome assessment	Low Risk	Any one of the following: <ul style="list-style-type: none"> No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High Risk	
	Unclear Risk	Any one of the following: <ul style="list-style-type: none"> No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding Blinding of outcome assessment, but likely that the blinding could have been broken and the outcome measurement is likely to be influenced by lack of blinding <p>Any one of the following:</p> <ul style="list-style-type: none"> Insufficient information to permit judgement of ‘Low risk’ or ‘High risk’ The study did not address this outcome
Incomplete data outcome	Low Risk	Any one of the following: <ul style="list-style-type: none"> No missing outcome data Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias) Missing outcome data balanced in numbers

		<p>across intervention groups, with similar reasons for missing data across groups</p> <ul style="list-style-type: none"> • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size • Missing data have been imputed using appropriate methods.
	High Risk	
	Unclear	<p>Any one of the following:</p> <ul style="list-style-type: none"> • Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size • ‘As-treated’ analysis done with substantial departure of the intervention received from that assigned at randomization • Potentially inappropriate application of simple imputation <p>Any one of the following:</p> <ul style="list-style-type: none"> • Insufficient reporting of attrition/exclusions to permit judgement of ‘Low risk’ or ‘High risk’ (e.g. number randomized not stated, no reasons for missing data provided) • The study did not address this outcome
Selective reporting	Low Risk	<p>Any of the following:</p> <ul style="list-style-type: none"> • The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	High Risk	<ul style="list-style-type: none"> • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)

	Unclear	<p>Any one of the following:</p> <ul style="list-style-type: none"> • Not all of the study's pre-specified primary outcomes have been reported • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect) • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis • The study report fails to include results for a key outcome that would be expected to have been reported for such a study <p>Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.</p>
Other bias	Low Risk	The study appears to be free of other sources of bias.
	High Risk	<p>There is at least one important risk of bias. For example, the study:</p> <ul style="list-style-type: none"> • Had a potential source of bias related to the specific study design used • Has been claimed to have been fraudulent • Had some other problem
	Unclear	<p>There may be a risk of bias, but there is either:</p> <ul style="list-style-type: none"> • Insufficient information to assess whether an important risk of bias exists • Insufficient rationale or evidence that an identified problem will introduce bias

Appendix 5: Morisky Medication Adherence Scale

(Please check one box on each line)

- | | <i>Yes</i> | <i>No</i> |
|--|-----------------------|-----------------------|
| 1. Do you ever forget to take Parkinson's disease medicine? | <input type="radio"/> | <input type="radio"/> |
| 2. Do you ever have problems remembering to take your Parkinson's disease medication? | <input type="radio"/> | <input type="radio"/> |
| 3. When you feel better, do you sometimes stop taking your Parkinson's disease medicine? | <input type="radio"/> | <input type="radio"/> |
| 4. Sometimes if you feel worse when you take your Parkinson's disease medicine, do you stop taking it? | <input type="radio"/> | <input type="radio"/> |

Appendix 6: Parkinson's Disease Questionnaire - 39 (PDQ-39)

11/04/11 Version 1.0

HEALTH SERVICES RESEARCH UNIT

DEPARTMENT OF PUBLIC HEALTH AND PRIMARY CARE
UNIVERSITY OF OXFORD

PDQ-39

Parkinson's Disease Quality of Life Questionnaire

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DUE TO HAVING PARKINSON'S DISEASE, how often have you experienced the following, during the last month?

Due to having Parkinson's disease, how often during the last month have you

*Please tick **one box** for each question*

	Never	Occasionally	Sometimes	Often	Always or cannot do at all
1. Had difficulty doing the leisure activities which you would like to do?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Had difficulty looking after your home, e.g. DIY, housework, cooking?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Had difficulty carrying bags of shopping?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Had problems walking half a mile?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Had problems walking 100 yards?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Had problems getting around the house as easily as you would like?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Had difficulty getting around in public?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Needed someone else to accompany you when you went out?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Felt frightened or worried about falling over in public?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Never	Occasionally	Sometimes	Often	Always
10. Been confined to the house more than you would like?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Had difficulty washing yourself?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. Had difficulty dressing yourself?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. Had problems doing up buttons or shoe laces?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. Had problems writing clearly?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. Had difficulty cutting up your food?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. Had difficulty holding a drink without spilling it?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. Felt depressed?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. Felt isolated and lonely?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. Felt weepy or tearful?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Never	Occasionally	Sometimes	Often	Always
20. Felt angry or bitter?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. Felt anxious?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. Felt worried about your future?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23. Felt you had to conceal your Parkinson's from people?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
24. Avoided situations which involve eating or drinking in public?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25. Felt embarrassed in public due to having Parkinson's disease?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26. Felt worried by other people's reaction to you?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27. Had problems with your close personal relationships?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
28. Lacked support in the ways you need from your spouse or partner? <i>If you do not have a spouse or partner, please tick here</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
29. Lacked support in the ways you need from your family or close friends?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Never	Occasionally	Sometimes	Often	Always
30. Unexpectedly fallen asleep during the day?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
31. Had problems with your concentration, e.g. when reading or watching TV?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
32. Felt your memory was bad?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
33. Had distressing dreams or hallucinations?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
34. Had difficulty with your speech?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
35. Felt unable to communicate with people properly?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
36. Felt ignored by people?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
37. Had painful muscle cramps or spasms?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
38. Had aches and pains in your joints or body?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
39. Felt unpleasantly hot or cold?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Appendix 7: MDS - Unified Parkinson's
Disease Rating Scale
(MDS - UPDRS)**

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

Overview: This portion of the scale assesses the non-motor impact of Parkinson's disease (PD) on patients' experiences of daily living. There are 13 questions. Part 1A is administered by the rater (six questions) and focuses on complex behaviors. Part 1B is a component of the self-administered Patient Questionnaire that covers seven questions on non-motor experiences of daily living.

Part 1A:

In administering Part 1A, the examiner should use the following guidelines:

1. Mark at the top of the form the primary data source as patient, caregiver, or patient and caregiver in equal proportion.
2. The response to each item should refer to a period encompassing the prior week including the day on which the information is collected.
3. All items must have an integer rating (no half points, no missing scores). In the event that an item does not apply or cannot be rated (e.g., amputee who cannot walk), the item is marked UR for Unable to Rate.
4. The answers should reflect the usual level of function and words such as "usually", "generally", "most of the time" can be used with patients.
5. Each question has a text for you to read (Instructions to patients/caregiver). After that statement, you can elaborate and probe based on the target symptoms outlined in the Instructions to examiner. You should NOT READ the RATING OPTIONS to the patient/caregiver, because these are written in medical terminology. From the interview and probing, you will use your medical judgment to arrive at the best response.
6. Patients may have co-morbidities and other medical conditions that can affect their function. You and the patient must rate the problem as it exists and do not attempt to separate elements due to Parkinson's disease from other conditions.

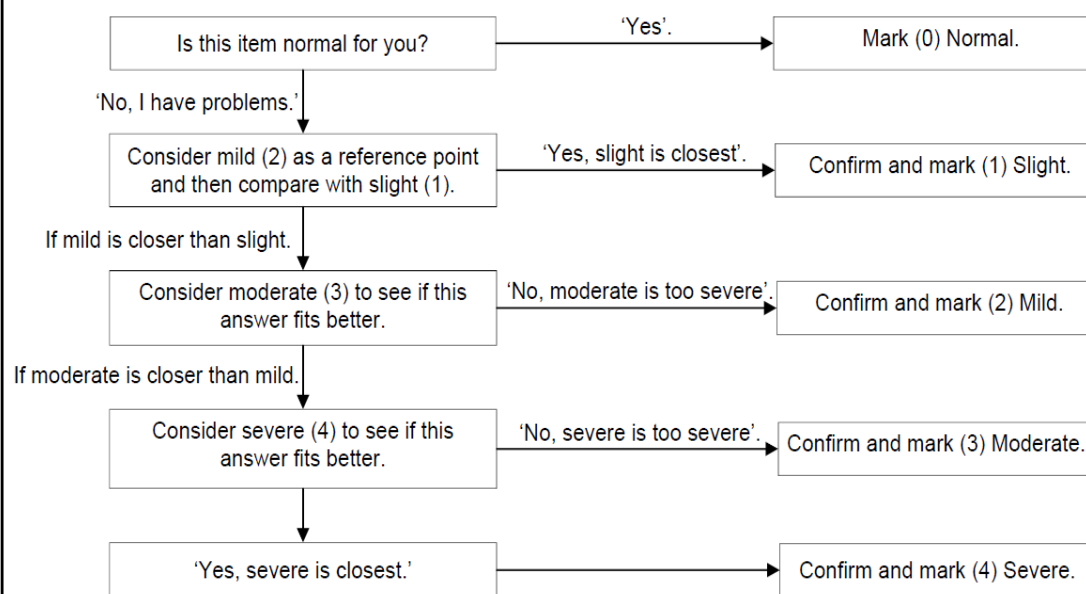
EXAMPLE OF NAVIGATING THROUGH THE RESPONSE OPTIONS FOR PART 1A

Suggested strategies for obtaining the most accurate answer:

After reading the instructions to the patient, you will need to probe the entire domain under discussion to determine Normal vs. problematic: If your questions do not identify any problem in this domain, record 0 and move on to the next question.

If your questions identify a problem in this domain, you should work next with a reference anchor at the mid-range (option 2 or Mild) to find out if the patient functions at this level, better or worse. You will not be reading the choices of responses to the patient as the responses use clinical terminology. You will be asking enough probing questions to determine the response that should be coded.

Work up and down the options with the patient to identify the most accurate response, giving a final check by excluding the options above and below the selected response.



1.2 HALLUCINATIONS AND PSYCHOSIS	SCORE
<p><u>Instructions to examiner:</u> Consider both illusions (misinterpretations of real stimuli) and hallucinations (spontaneous false sensations). Consider all major sensory domains (visual, auditory, tactile, olfactory and gustatory). Determine presence of unformed (for example sense of presence or fleeting false impressions) as well as formed (fully developed and detailed) sensations. Rate the patients insight into hallucinations and identify delusions and psychotic thinking.</p> <p><u>Instructions to patients [and caregiver]:</u> Over the past week have you seen, heard, smelled or felt things that were not really there? [If yes, examiner asks patient or caregiver to elaborate and probes for information]</p> <p>0: Normal: No hallucinations or psychotic behaviour.</p> <p>1: Slight: Illusions or non-formed hallucinations, but patient recognizes them without loss of insight.</p> <p>2: Mild: Formed hallucinations independent of environmental stimuli. No loss of insight.</p> <p>3: Moderate: Formed hallucinations with loss of insight.</p> <p>4: Severe: Patient has delusions or paranoia.</p>	<input data-bbox="1366 584 1430 658" type="text"/>
<p>1.3 DEPRESSED MOOD</p> <p><u>Instructions to examiner:</u> Consider low mood, sadness, hopelessness, feelings of emptiness or loss of enjoyment. Determine their presence and duration over the past week and rate their interference with the patient's ability to carry out daily routines and engage in social interactions.</p> <p><u>Instruction to the patient (and caregiver):</u> Over the past week have you felt low, sad, hopeless or unable to enjoy things? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you carry out your usual activities or to be with people? If yes, examiner asks patient or caregiver to elaborate and probes for information]</p> <p>0: Normal: No depressed mood.</p> <p>1: Slight: Episodes of depressed mood that are not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions.</p> <p>2: Mild: Depressed mood that is sustained over days, but without interference with normal activities and social interactions.</p> <p>3: Moderate: Depressed mood that interferes with, but does not preclude, the patient's ability to carry out normal activities and social interactions.</p> <p>4: Severe: Depressed mood precludes patient's ability to carry out normal activities and social interactions.</p>	<input data-bbox="1366 1429 1430 1503" type="text"/>

1.4 ANXIOUS MOOD	SCORE
<p><u>Instructions to examiner:</u> Determine nervous, tense, worried or anxious feelings (including panic attacks) over the past week and rate their duration and interference with the patient's ability to carry out daily routines and engage in social interactions.</p> <p><u>Instructions to patients [and caregiver]:</u> Over the past week have you felt nervous, worried or tense? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you to follow your usual activities or to be with other people? [If yes, examiner asks patient or caregiver to elaborate and probes for information.]</p> <p>0: Normal: No anxious feelings.</p> <p>1: Slight: Anxious feelings present but not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions.</p> <p>2: Mild: Anxious feelings are sustained over more than one day at a time, but without interference with patient's ability to carry out normal activities and social interactions.</p> <p>3: Moderate: Anxious feelings interfere with, but do not preclude, the patient's ability to carry out normal activities and social interactions.</p> <p>4: Severe: Anxious feelings preclude patient's ability to carry out normal activities and social interactions.</p>	<input data-bbox="1394 591 1458 667" type="text"/>
<p>1.5 APATHY</p> <p><u>Instructions to examiner:</u> Consider level of spontaneous activity, assertiveness, motivation and initiative and rate the impact of reduced levels on performance of daily routines and social interactions. Here the examiner should attempt to distinguish between apathy and similar symptoms that are best explained by depression.</p> <p><u>Instructions to patients (and caregiver):</u> Over the past week, have you felt indifferent to doing activities or being with people? If yes, examiner asks patient or caregiver to elaborate and probes for information.]</p> <p>0: Normal: No apathy.</p> <p>1: Slight: Apathy appreciated by patient and/or caregiver, but no interference with daily activities and social interactions.</p> <p>2: Mild: Apathy interferes with isolated activities and social interactions.</p> <p>3: Moderate: Apathy interferes with most activities and social interactions.</p> <p>4: Severe: Passive and withdrawn, complete loss of initiative.</p>	<input data-bbox="1394 1496 1458 1572" type="text"/>

1.6 FEATURES OF DOPAMINE DYSREGULATION SYNDROME

SCORE

Instructions to examiner: Consider involvement in a variety of activities including atypical or excessive gambling (e.g. casinos or lottery tickets), atypical or excessive sexual drive or interests (e.g., unusual interest in pornography, masturbation, sexual demands on partner), other repetitive activities (e.g. hobbies, dismantling objects, sorting or organizing), or taking extra non-prescribed medication for non-physical reasons (i.e., addictive behavior). Rate the impact of such abnormal activities/behaviors on the patient's personal life and on his family and social relations (including need to borrow money or other financial difficulties like withdrawal of credit cards, major family conflicts, lost time from work, or missed meals or sleep because of the activity).

Instructions to patients [and caregiver]: Over the past week, have you had unusually strong urges that are hard to control? Do you feel driven to do or think about something and find it hard to stop? [Give patient examples such as gambling, cleaning, using the computer, taking extra medicine, obsessing about food or sex, all depending on the patients.

- 0: Normal: No problems present.
- 1: Slight: Problems are present but usually do not cause any difficulties for the patient or family/caregiver.
- 2: Mild: Problems are present and usually cause a few difficulties in the patient's personal and family life.
- 3: Moderate: Problems are present and usually cause a lot of difficulties in the patient's personal and family life.
- 4: Severe: Problems are present and preclude the patient's ability to carry out normal activities or social interactions or to maintain previous standards in personal and family life.

The remaining questions in Part I (Non-motor Experiences of Daily Living) [Sleep, Daytime Sleepiness, Pain and Other Sensation, Urinary Problems, Constipation Problems, Lightheadedness on Standing, and Fatigue] are in the **Patient Questionnaire** along with all questions in Part II [Motor Experiences of Daily Living].

Patient Questionnaire:

Instructions:

This questionnaire will ask you about your experiences of daily living.

There are 20 questions. We are trying to be thorough, and some of these questions may therefore not apply to you now or ever. If you do not have the problem, simply mark 0 for NO.

Please read each one carefully and read all answers before selecting the one that best applies to you.

We are interested in your average or usual function over the past week including today. Some patients can do things better at one time of the day than at others. However, only one answer is allowed for each question, so please mark the answer that best describes what you can do most of the time.

You may have other medical conditions besides Parkinson's disease. Do not worry about separating Parkinson's disease from other conditions. Just answer the question with your best response.

Use only 0, 1, 2, 3, 4 for answers, nothing else. Do not leave any blanks.

Your doctor or nurse can review the questions with you, but this questionnaire is for patients to complete, either alone or with their caregivers.

Who is filling out this questionnaire (check the best answer):

Patient

Caregiver

Patient and Caregiver in Equal Proportion

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

	SCORE
<p>1.7 SLEEP PROBLEMS</p> <p>Over the past week, have you had trouble going to sleep at night or staying asleep through the night? Consider how rested you felt after waking up in the morning.</p> <p>0: Normal: No problems.</p> <p>1: Slight: Sleep problems are present but usually do not cause trouble getting a full night of sleep.</p> <p>2: Mild: Sleep problems usually cause some difficulties getting a full night of sleep.</p> <p>3: Moderate: Sleep problems cause a lot of difficulties getting a full night of sleep, but I still usually sleep for more than half the night.</p> <p>4: Severe: I usually do not sleep for most of the night.</p>	<input data-bbox="1394 680 1461 757" type="text"/>
<p>1.8 DAYTIME SLEEPINESS</p> <p>Over the past week, have you had trouble staying awake during the daytime?</p> <p>0: Normal: No daytime sleepiness.</p> <p>1: Slight: Daytime sleepiness occurs but I can resist and I stay awake.</p> <p>2: Mild: Sometimes I fall asleep when alone and relaxing. For example, while reading or watching TV.</p> <p>3: Moderate: I sometimes fall asleep when I should not. For example, while eating or talking with other people.</p> <p>4: Severe: I often fall asleep when I should not. For example, while eating or talking with other people.</p>	<input data-bbox="1394 1503 1461 1579" type="text"/>

	SCORE
<p>1.9 PAIN AND OTHER SENSATIONS</p> <p>Over the past week, have you had uncomfortable feelings in your body like pain, aches tingling or cramps?</p> <p>0: Normal: No uncomfortable feelings.</p> <p>1: Slight: I have these feelings. However, I can do things and be with other people without difficulty.</p> <p>2: Mild: These feelings cause some problems when I do things or am with other people.</p> <p>3: Moderate: These feelings cause a lot of problems, but they do not stop me from doing things or being with other people.</p> <p>4: Severe: These feelings stop me from doing things or being with other people.</p>	<input data-bbox="1393 595 1458 674" type="text"/>
<p>1.10 URINARY PROBLEMS</p> <p>Over the past week, have you had trouble with urine control? For example, an urgent need to urinate, a need to urinate too often, or urine accidents?</p> <p>0: Normal: No urine control problems.</p> <p>1: Slight: I need to urinate often or urgently. However, these problems do not cause difficulties with my daily activities.</p> <p>2: Mild: Urine problems cause some difficulties with my daily activities. However, I do not have urine accidents.</p> <p>3: Moderate: Urine problems cause a lot of difficulties with my daily activities, including urine accidents.</p> <p>4: Severe: I cannot control my urine and use a protective garment or have a bladder tube.</p>	<input data-bbox="1393 1469 1458 1547" type="text"/>

	SCORE
<p>1.11 CONSTIPATION PROBLEMS</p> <p>Over the past week have you had constipation troubles that cause you difficulty moving your bowels?</p> <p>0: Normal: No constipation.</p> <p>1: Slight: I have been constipated. I use extra effort to move my bowels. However, this problem does not disturb my activities or my being comfortable.</p> <p>2: Mild: Constipation causes me to have some troubles doing things or being comfortable.</p> <p>3: Moderate: Constipation causes me to have a lot of trouble doing things or being comfortable. However, it does not stop me from doing anything.</p> <p>4: Severe: I usually need physical help from someone else to empty my bowels.</p>	<input data-bbox="1394 598 1460 676" type="checkbox"/>
<p>1.12 LIGHT HEADEDNESS ON STANDING</p> <p>Over the past week, have you felt faint, dizzy or foggy when you stand up after sitting or lying down?</p> <p>0: Normal: No dizzy or foggy feelings.</p> <p>1: Slight: Dizzy or foggy feelings occur. However, they do not cause me troubles doing things.</p> <p>2: Mild: Dizzy or foggy feelings cause me to hold on to something, but I do not need to sit or lie back down.</p> <p>3: Moderate: Dizzy or foggy feelings cause me to sit or lie down to avoid fainting or falling.</p> <p>4: Severe: Dizzy or foggy feelings cause me to fall or faint.</p>	<input data-bbox="1394 1487 1460 1565" type="checkbox"/>

	SCORE
<p>2.2 SALIVA & DROOLING</p> <p>Over the past week, have you usually had too much saliva during when you are awake or when you sleep?</p> <p>0: Normal: Not at all (no problems).</p> <p>1: Slight: I have too much saliva, but do not drool.</p> <p>2: Mild: I have some drooling during sleep, but none when I am awake.</p> <p>3: Moderate: I have some drooling when I am awake, but I usually do not need tissues or a handkerchief.</p> <p>4: Severe: I have so much drooling that I regularly need to use tissues or a handkerchief to protect my clothes.</p>	<input data-bbox="1412 600 1476 683" type="checkbox"/>
<p>2.3 CHEWING AND SWALLOWING</p> <p>Over the past week, have you usually had problems swallowing pills or eating meals? Do you need your pills cut or crushed or your meals to be made soft, chopped or blended to avoid choking?</p> <p>0: Normal: No problems.</p> <p>1: Slight: I am aware of slowness in my chewing or increased effort at swallowing, but I do not choke or need to have my food specially prepared.</p> <p>2: Mild: I need to have my pills cut or my food specially prepared because of chewing or swallowing problems, but I have not choked over the past week.</p> <p>3: Moderate. I choked at least once in the past week.</p> <p>4: Severe: Because of chewing and swallowing problems, I need a feeding tube.</p>	<input data-bbox="1412 1460 1476 1543" type="checkbox"/>

	SCORE
<p>2.4 EATING TASKS</p> <p>Over the past week, have you usually had troubles handling your food and using eating utensils? For example, do you have trouble handling finger foods or using forks, knives, spoons, chopsticks?</p> <p>0: Normal: Not at all (No problems).</p> <p>1: Slight: I am slow, but I do not need any help handling my food and have not had food spills while eating.</p> <p>2: Mild: I am slow with my eating and have occasional food spills. I may need help with a few tasks such as cutting meat.</p> <p>3: Moderate: I need help with many eating tasks but can manage some alone.</p> <p>4: Severe: I need help for most or all eating tasks.</p>	<input data-bbox="1398 600 1461 678" type="checkbox"/>
<p>2.5 DRESSING</p> <p>Over the past week, have you usually had problems dressing? For example, are you slow or do you need help with buttoning, using zippers, putting on or taking off your clothes or jewelry?</p> <p>0: Normal: Not at all (no problems).</p> <p>1: Slight: I am slow but I do not need help.</p> <p>2: Mild: I am slow and need help for a few dressing tasks (buttons, bracelets).</p> <p>3: Moderate: I need help for many dressing tasks.</p> <p>4: Severe: I need help for most or all dressing tasks.</p>	<input data-bbox="1398 1473 1461 1552" type="checkbox"/>

2.6 HYGIENE	SCORE
<p>Over the past week, have you usually been slow or do you need help with washing, bathing, shaving, brushing teeth, combing your hair or with other personal hygiene?</p> <p>0: Normal: Not at all (no problems).</p> <p>1: Slight: I am slow but I do not need any help.</p> <p>2: Mild: I need someone else to help me with some hygiene tasks.</p> <p>3: Moderate: I need help for many hygiene tasks.</p> <p>4: Severe: I need help for most or all of my hygiene tasks.</p>	<input data-bbox="1390 450 1453 528" type="checkbox"/>
<p>2.7 HANDWRITING</p> <p>Over the past week, have people usually had trouble reading your handwriting?</p> <p>0: Normal: Not at all (no problems).</p> <p>1: Slight: My writing is slow, clumsy or uneven, but all words are clear.</p> <p>2: Mild: Some words are unclear and difficult to read.</p> <p>3: Moderate: Many words are unclear and difficult to read.</p> <p>4: Severe: Most or all words cannot be read.</p>	<input data-bbox="1390 1055 1453 1133" type="checkbox"/>
<p>2.8 DOING HOBBIES AND OTHER ACTIVITIES</p> <p>Over the past week, have you usually had trouble doing your hobbies or other things that you like to do?</p> <p>0: Normal: Not at all (no problems).</p> <p>1: Slight: I am a bit slow but do these activities easily.</p> <p>2: Mild: I have some difficulty doing these activities.</p> <p>3: Moderate: I have major problems doing these activities, but still do most.</p> <p>4: Severe: I am unable to do most or all of these activities.</p>	<input data-bbox="1390 1648 1453 1727" type="checkbox"/>

	SCORE
<p>2.9 TURNING IN BED</p> <p>Over the past week, do you usually have trouble turning over in bed?</p> <p>0: Normal: Not at all (no problems).</p> <p>1: Slight: I have a bit of trouble turning, but I do not need any help.</p> <p>2: Mild: I have a lot of trouble turning and need occasional help from someone else.</p> <p>3: Moderate: To turn over I often need help from someone else.</p> <p>4: Severe: I am unable to turn over without help from someone else.</p>	<input data-bbox="1396 443 1460 526" type="checkbox"/>
<p>2.10 TREMOR</p> <p>Over the past week, have you usually had shaking or tremor?</p> <p>0: Normal: Not at all. I have no shaking or tremor.</p> <p>1: Slight: Shaking or tremor occurs but does not cause problems with any activities.</p> <p>2: Mild: Shaking or tremor causes problems with only a few activities.</p> <p>3: Moderate: Shaking or tremor causes problems with many of my daily activities.</p> <p>4: Severe: Shaking or tremor causes problems with most or all activities.</p>	<input data-bbox="1396 1030 1460 1113" type="checkbox"/>
<p>2.11 GETTING OUT OF BED, A CAR, OR A DEEP CHAIR</p> <p>Over the past week, have you usually had trouble getting out of bed, a car seat, or a deep chair?</p> <p>0: Normal: Not at all (no problems).</p> <p>1: Slight: I am slow or awkward, but I usually can do it on my first try.</p> <p>2: Mild: I need more than one try to get up or need occasional help.</p> <p>3: Moderate: I sometimes need help to get up, but most times I can still do it on my own.</p> <p>4: Severe: I need help most or all of the time.</p>	<input data-bbox="1396 1624 1460 1706" type="checkbox"/>

	SCORE
<p>2.12 WALKING AND BALANCE</p> <p>Over the past week, have you usually had problems with balance and walking?</p> <p>0: Normal: Not at all (no problems).</p> <p>1: Slight: I am slightly slow or may drag a leg. I never use a walking aid.</p> <p>2: Mild: I occasionally use a walking aid, but I do not need any help from another person.</p> <p>3: Moderate: I usually use a walking aid (cane, walker) to walk safely without falling. However, I do not usually need the support of another person.</p> <p>4: Severe: I usually use the support of another persons to walk safely without falling.</p>	<input data-bbox="1391 495 1457 573" type="checkbox"/>
<p>2.13 FREEZING</p> <p>Over the past week, on your usual day when walking, do you suddenly stop or freeze as if your feet are stuck to the floor.</p> <p>0: Normal: Not at all (no problems).</p> <p>1: Slight: I briefly freeze but I can easily start walking again. I do not need help from someone else or a walking aid (cane or walker) because of freezing.</p> <p>2: Mild: I freeze and have trouble starting to walk again, but I do not need someone's help or a walking aid (cane or walker) because of freezing.</p> <p>3: Moderate: When I freeze I have a lot of trouble starting to walk again and, because of freezing, I sometimes need to use a walking aid or need someone else's help.</p> <p>4: Severe: Because of freezing, most or all of the time, I need to use a walking aid or someone's help.</p>	<input data-bbox="1391 1238 1457 1317" type="checkbox"/>
<p style="text-align: center;">This completes the questionnaire. We may have asked about problems you do not even have, and may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this questionnaire.</p>	

Part IV: Motor Complications

Overview and Instructions: In this section, the rater uses historical and objective information to assess two motor complications, dyskinesias and motor fluctuations that include OFF-state dystonia. Use all information from patient, caregiver, and the examination to answer the six questions that summarize function over the past week including today. As in the other sections, rate using only integers (no half points allowed) and leave no missing ratings. If the item cannot be rated, place UR for Unable to Rate. You will need to choose some answers based on percentages, and therefore you will need to establish how many hours generally are awake hours and use this figure as the denominator for "OFF" time and Dyskinesias. For "OFF dystonia", the total "Off" time will be the denominator. Operational definitions for examiner's use.

Dyskinesias: Involuntary random movements

Words that patients often recognize for dyskinesias include "irregular jerking", "wiggling", "twitching". It is essential to stress to the patient the difference between dyskinesias and tremor, a common error when patients are assessing dyskinesias.

Dystonia: contorted posture, often with a twisting component:

Words that patients often recognize for dystonia include "spasms", "cramps", "posture".

Motor fluctuation: Variable response to medication:

Words that patients often recognize for motor fluctuation include "wearing out", "wearing off", "roller-coaster effect", "on-off", "uneven medication effects".

OFF: Typical functional state when patients have a poor response in spite of taking medication or the typical functional response when patients are on NO treatment for parkinsonism. Words that patients often recognize include "low time", "bad time", "shaking time", "slow time", "time when my medications don't work."

ON: Typical functional state when patients are receiving medication and have a good response:

Words that patients often recognize include "good time", "walking time", "time when my medications work."

A . DYSKINESIAS [exclusive of OFF-state dystonia]

4.1 TIME SPENT WITH DYSKINESIAS

Instructions to examiner: Determine the hours in the usual waking day and then the hours of dyskinesias. Calculate the percentage. If the patient has dyskinesias in the office, you can point them out as a reference to ensure that patients and caregivers understand what they are rating. You may also use your own acting skills to enact the dyskinetic movements you have seen in the patient before or show them dyskinetic movements typical of other patients. Exclude from this question early morning and nighttime painful dystonia.

Instructions to patient [and caregiver]. Over the past week, how many hours do you usually sleep on a daily basis, including nighttime sleep and daytime napping? Alright, if you sleep ___ hrs, you are awake ___ hrs. Out of those awake hours, how many hours in total do you have wiggling, twitching or jerking movements? Do not count the times when you have tremor, which is a regular back and forth shaking or times when you have painful foot cramps or spasms in the early morning or at nighttime. I will ask about those later. Concentrate only on these types of wiggling, jerking and irregular movements. Add up all the time during the waking day when these usually occur. How many hours ___ (use this number for your calculation).

- 0: Normal: No dyskinesias.
- 1: Slight: ≤ 25% of waking day.
- 2: Mild: 26 - 50% of waking day.
- 3: Moderate: 51 - 75% of waking day.
- 4: Severe: > 75% of waking day.

- | | |
|---------------------------------|-------|
| 1. Total Hours Awake: | _____ |
| 2. Total Hours with Dyskinesia: | _____ |
| 3. % Dyskinesia = ((2/1)*100): | _____ |

SCORE

4.2 FUNCTIONAL IMPACT OF DYSKINESIAS	SCORE
<p>Instructions to examiner: Determine the degree to which dyskinesias impact on the patient's daily function in terms of activities and social interactions. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer.</p> <p><i>Instructions to patient [and caregiver]: Over the past week, did you usually have trouble doing things or being with people when these jerking movements occurred? Did they stop you from doing things or from being with people?</i></p> <p>0: Normal: No dyskinesias or no impact by dyskinesias on activities or social interactions.</p> <p>1: Slight: Dyskinesias impact on a few activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.</p> <p>2: Mild: Dyskinesias impact on many activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.</p> <p>3: Moderate: Dyskinesias impact on activities to the point that the patient usually does not perform some activities or does not usually participate in some social activities during dyskinetic episodes.</p> <p>4: Severe: Dyskinesias impact on function to the point that the patient usually does not perform most activities or participate in most social interactions during dyskinetic episodes.</p>	<input style="width: 40px; height: 40px; border: 1px solid black;" type="text"/>

B . MOTOR FLUCTUATIONS

4.3 TIME SPENT IN THE OFF STATE	SCORE						
<p>Instructions to examiner: Use the number of waking hours derived from 4.1 and determine the hours spent in the "OFF" state. Calculate the percentage. If the patient has an OFF period in the office, you can point to this state as a reference. You may also use your knowledge of the patient to describe a typical OFF period. Additionally you may use your own acting skills to enact an OFF period you have seen in the patient before or show them OFF function typical of other patients. Mark down the typical number of OFF hours, because you will need this number for completing 4.6</p> <p><i>Instructions to patient [and caregiver]: Some patients with Parkinson's disease have a good effect from their medications throughout their awake hours and we call that "ON" time. Other patients take their medications but still have some hours of low time, bad time, slow time or shaking time. Doctors call these low periods "OFF" time. Over the past week, you told me before that you are generally awake ___ hrs each day. Out of these awake hours, how many hours in total do you usually have this type of low level or OFF function ___ (Use this number for your calculations).</i></p> <p>0: Normal: No OFF time.</p> <p>1: Slight: ≤ 25% of waking day.</p> <p>2: Mild: 26 - 50% of waking day.</p> <p>3: Moderate: 51 - 75% of waking day.</p> <p>4: Severe: > 75% of waking day.</p>	<input style="width: 40px; height: 40px; border: 1px solid black;" type="text"/>						
<table border="1" style="margin-left: auto;"> <tr> <td style="padding: 5px;">1. Total Hours Awake:</td> <td style="padding: 5px;">_____</td> </tr> <tr> <td style="padding: 5px;">2. Total Hours OFF:</td> <td style="padding: 5px;">_____</td> </tr> <tr> <td style="padding: 5px;">3. % OFF = ((2/1)*100):</td> <td style="padding: 5px;">_____</td> </tr> </table>		1. Total Hours Awake:	_____	2. Total Hours OFF:	_____	3. % OFF = ((2/1)*100):	_____
1. Total Hours Awake:	_____						
2. Total Hours OFF:	_____						
3. % OFF = ((2/1)*100):	_____						

4.4 FUNCTIONAL IMPACT OF FLUCTUATIONS	SCORE
<p><u>Instructions to examiner:</u> Determine the degree to which motor fluctuations impact on the patient's daily function in terms of activities and social interactions. This question concentrates on the difference between the ON state and the OFF state. If the patient has no OFF time, the rating must be 0, but if patients have very mild fluctuations, it is still possible to be rated 0 on this item if no impact on activities occurs. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer.</p> <p><u>Instructions to patient [and caregiver]:</u> Think about when those low or "OFF" periods have occurred over the past week. Do you usually have more problems doing things or being with people than compared to the rest of the day when you feel your medications working? Are there some things you usually do during a good period that you have trouble with or stop doing during a low period?</p> <p>0: Normal: No fluctuations or No impact by fluctuations on performance of activities or social interactions.</p> <p>1: Slight: Fluctuations impact on a few activities, but during OFF, the patient usually performs all activities and participates in all social interactions that typically occur during the ON state.</p> <p>2: Mild: Fluctuations impact many activities, but during OFF, the patient still usually performs all activities and participates in all social interactions that typically occur during the ON state.</p> <p>3: Moderate: Fluctuations impact on the performance of activities during OFF to the point that the patient usually does not perform some activities or participate in some social interactions that are performed during ON periods.</p> <p>4: Severe: Fluctuations impact on function to the point that, during OFF, the patient usually does not perform most activities or participate in most social interactions that are performed during ON periods.</p>	<input data-bbox="1391 678 1455 757" type="text"/>
<p>4.5 COMPLEXITY OF MOTOR FLUCTUATIONS</p> <p><u>Instructions to examiner:</u> Determine the usual predictability of OFF function whether due to dose, time of day, food intake or other factors. Use the information provided by the patients and caregiver and supplement with your own observations. You will ask if the patient can count on them always coming at a special time, mostly coming at a special time (in which case you will probe further to separate slight from mild), only sometimes coming at a special time or are they totally unpredictable? Narrowing down the percentage will allow you to find the correct answer.</p> <p><u>Instructions to patient [and caregiver]:</u> For some patients, the low or "OFF" periods happen at certain times during day or when they do activities like eating or exercising. Over the past week, do you usually know when your low periods will occur? In other words, do your low periods <u>always</u> come at a certain time? Do they <u>mostly</u> come at a certain time? Do they <u>only sometimes</u> come at a certain time? Are your low periods totally unpredictable?"</p> <p>0: Normal: No motor fluctuations.</p> <p>1: Slight: OFF times are predictable all or almost all of the time (> 75%).</p> <p>2: Mild: OFF times are predictable most of the time (51-75%).</p> <p>3: Moderate: OFF times are predictable some of the time (26-50%).</p> <p>4: Severe: OFF episodes are rarely predictable. (≤ 25%).</p>	<input data-bbox="1391 1552 1455 1630" type="text"/>

C. "OFF" DYSTONIA

4.6 PAINFUL OFF-STATE DYSTONIA

Instructions to examiner: For patients who have motor fluctuations, determine what proportion of the OFF episodes usually includes painful dystonia? You have already determined the number of hours of "OFF" time (4.3). Of these hours, determine how many are associated with dystonia and calculate the percentage. If there is no OFF time, mark 0.

Instructions to patient [and caregiver]: In one of the questions I asked earlier, you said you generally have ___ hours of low or "OFF" time when your Parkinson's disease is under poor control. During these low or "OFF" periods, do you usually have painful cramps or spasms? Out of the total ___ hrs of this low time, if you add up all the time in a day when these painful cramps come, how many hours would this make?

- 0: Normal: No dystonia OR NO OFF TIME.
- 1: Slight: < 25% of time in OFF state.
- 2: Mild: 26-50% of time in OFF state.
- 3: Moderate: 51-75% of time in OFF state.
- 4: Severe: > 75% of time in OFF state.

- | | |
|----------------------------------|-------|
| 1. Total Hours Off: | _____ |
| 2. Total Off Hours w/Dystonia: | _____ |
| 3. % Off Dystonia = ((2/1)*100): | _____ |



Summary statement to patient: READ TO PATIENT

This completes my rating of your Parkinson's disease. I know the questions and tasks have taken several minutes, but I wanted to be complete and cover all possibilities. In doing so, I may have asked about problems you do not even have, and I may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this scale with me.

Appendix 8: Beliefs About Medication Questionnaire (BMQ)

**YOUR VIEWS ABOUT
MEDICINES PRESCRIBED FOR YOU**

- We would like to ask you about your personal views about medicines prescribed for you.
- These are statements other people have made about their medicines.
- Please show how much you agree or disagree with them by ticking the appropriate box.

**There are no right or wrong answers.
We are interested in your personal views**

	Views about MEDICINES PRESCRIBED FOR YOU:	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
BS1	My health, at present, depends on my medicines					
BS2	Having to take medicines worries me					
BS3	My life would be impossible without my medicines					
BS5	I sometimes worry about long-term effects of my medicines					
BS4	Without my medicines I would be very ill					
BS6	My medicines are a mystery to me					
BS7	My health in the future will depend on my medicines					
BS8	My medicines disrupt my life					
BS9	I sometimes worry about becoming too dependent on my medicines					
BS10	My medicines protect me from becoming worse					
BS11	These medicine give me unpleasant side effects					

**YOUR VIEWS ABOUT
MEDICINES IN GENERAL**

- These are statements that other people have made about medicines in general.
- Please show how much you agree or disagree with them by ticking the appropriate box.

	Views about MEDICINES IN GENERAL	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
BG1	Doctors use too many medicines					
BG2	People who take medicines should stop their treatment for a while every now and again					
BG3	Most medicines are addictive					
BG4	Natural remedies are safer than medicines					
BG5	Medicines do more harm than good					
BG6	All medicines are poisons					
BG7	Doctors place too much trust on medicines					
BG8	If doctors had more time with patients they would prescribe fewer medicines					

Appendix 9: EuroQol (EQ-5D)



Assigned Clinic Number:

CRTU Randomisation Number:

Health Questionnaire

English version for the UK

(validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about

I have some problems in walking about

I am confined to bed

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

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

Pain/Discomfort

I have no pain or discomfort

I have moderate pain or discomfort

I have extreme pain or discomfort

Anxiety/Depression

I am not anxious or depressed

I am moderately anxious or depressed

I am extremely anxious or depressed

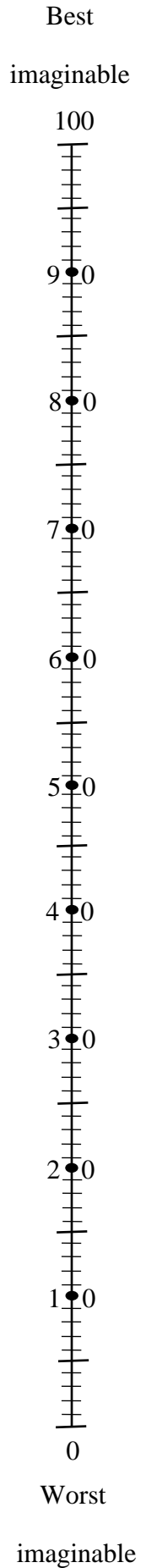
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

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

|

|

**Your own
health state
today**



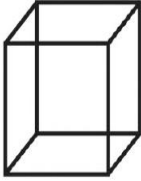
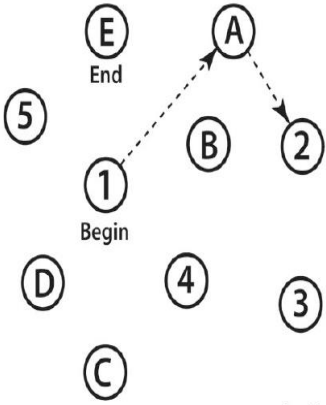
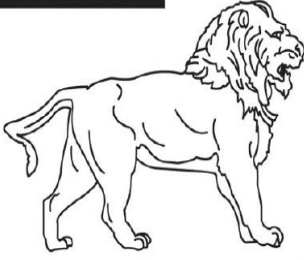
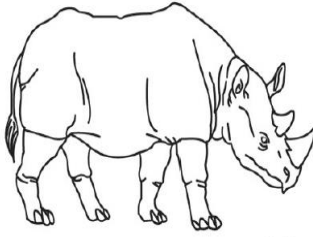
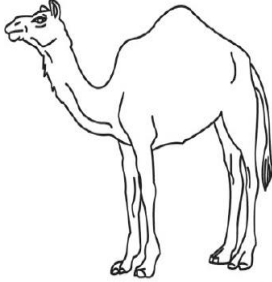
Appendix 10: Caregiving Distress Scale (CDS)

Appendix 11: Montreal Cognitive Assessment Scale (MoCA)

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME: _____
Education: _____
Sex: _____

Date of birth: _____
DATE: _____

VISUOSPATIAL / EXECUTIVE			Copy cube []	Draw CLOCK (Ten past eleven) (3 points) []	POINTS ___/5						
		[]		Contour [] Numbers [] Hands []	___/5						
NAMING											
											
[]		[]		[] ___/3							
MEMORY											
Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.			FACE	VELVET	CHURCH	DAISY	RED	No points			
1st trial											
2nd trial											
ATTENTION											
Read list of digits (1 digit/ sec.).		Subject has to repeat them in the forward order		[] 2 1 8 5 4		Subject has to repeat them in the backward order		[] 7 4 2			
Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors		[] FBACMNAAJKLBAFAKDEAAAJAMOF AAB		___/1		Serial 7 subtraction starting at 100		[] 93 [] 86 [] 79 [] 72 [] 65			
		4 or 5 correct subtractions: 3 pts , 2 or 3 correct: 2 pts , 1 correct: 1 pt , 0 correct: 0 pt		___/3		LANGUAGE		Repeat: I only know that John is the one to help today. []			
		The cat always hid under the couch when dogs were in the room. []		___/2		Fluency / Name maximum number of words in one minute that begin with the letter F		[] ____ (N ≥ 11 words)			
		[] ____		___/1		ABSTRACTION		Similarity between e.g. banana - orange = fruit [] train - bicycle [] watch - ruler			
		[] ____		___/2		DELAYED RECALL		Has to recall words WITH NO CUE			
		FACE []		VELVET []		CHURCH []		DAISY []			
		RED []		Points for UNCUED recall only		Optional		Category cue			
		Multiple choice cue		[]		[]		[]			
		[]		[]		[]		[]			
ORIENTATION											
[] Date		[] Month		[] Year		[] Day		[] Place [] City			
[]		[]		[]		[]		[]			
© Z.Nasreddine MD						www.mocatest.org		Normal ≥ 26 / 30		TOTAL ___/30	
Administered by: _____								Add 1 point if ≤ 12 yr edu			

Appendix 12: Hospital Anxiety & Depression Scale (HADS)

Hospital Anxiety and Depression Scale (HADS)



Name: _____ Date: _____

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

A	D			A	D
3		I feel tense or 'wound up'	I feel as if I am slowed down	3	
2		Most of the time	Nearly all the time	2	
1		A lot of the time	Very often	1	
0		From time to time, occasionally	Sometimes	0	
		Not at all	Not at all		
	0	I still enjoy the things I used to enjoy	I get a sort of frightened feeling like 'butterflies' in the stomach	0	
	1	Definitely as much	Not at all	1	
	2	Not quite so much	Occasionally	2	
	3	Only a little	Quite often	3	
		Hardly at all	Very often		
3		I get a sort of frightened feeling as if something awful is about to happen	I have lost interest in my appearance	3	
2		Very definitely and quite badly	Definitely	2	
1		Yes, but not too badly	I don't take as much care as I should	1	
0		A little, but it doesn't worry me	I may not take quite as much care	0	
		Not at all	I take just as much care as ever		
	0	I can laugh and see the funny side of things	I feel restless as if I have to be on the move	3	
	1	As much as I always could	Very much indeed	2	
	2	Not quite so much now	Quite a lot	1	
	3	Definitely not so much now	Not very much	0	
		Not at all	Not at all		
3		Worrying thoughts go through my mind	I look forward with enjoyment to things	0	
2		A great deal of the time	As much as I ever did	1	
1		A lot of the time	Rather less than I used to	2	
0		Not too often	Definitely less than I used to	3	
		Very little	Hardly at all		
	3	I feel cheerful	I get sudden feelings of panic	3	
	2	Never	Very often indeed	2	
	1	Not often	Quite often	1	
	0	Sometimes	Not very often	0	
		Most of the time	Not at all		
0		I can sit at ease and feel relaxed	I can enjoy a good book or radio or television programme	0	
1		Definitely	Often	1	
2		Usually	Sometimes	2	
3		Not often	Not often	3	
		Not at all	Very seldom		

Now check that you have answered all the questions

	A	D	
<p>This form is printed in green. Any other colour is an unauthorized photocopy.</p> <p>HADS copyright © R.P. Snaith and A.S. Zigmond, 1983, 1992, 1994.</p> <p>Record form items originally published in <i>Acta Psychiatrica Scandinavica</i> 67, 361-70, copyright © Munksgaard International Publishers Ltd, Copenhagen, 1983.</p> <p>First published in 1994 by nferNelson Publishing Company Ltd.</p> <p>Published by GL Assessment Limited, 389 Chiswick High Road, 9th Floor East, London W4 4AL.</p> <p>GL Assessment is part of the Granada Group</p> <p>Printed in Great Britain</p>	<table border="1" style="width: 100%; height: 20px;"> <tr> <td style="width: 50%;"></td> <td style="width: 50%;"></td> </tr> </table>		
<p>Code 0090002511</p>	<p>TOTAL</p>	<p>11(5.11)</p>	

Appendix 13: Information Hand-out for Moderate/Severe Depression



Movement Disorder Clinic,
Medicine for the Elderly
Norfolk and Norwich University Hospital
Tel: 01603 288173

The use of carer assisted adherence therapy for people with Parkinson's disease and their carers.

Dear

When you completed the Hospital Anxiety and Depression Scale as part of the above titled study, your score indicated that you may be suffering from depression. We will send a letter to your GP also giving them this information.

Depression is a common condition. About one in six people will experience depression during their lifetime. (NHS Direct 2010)

It can affect anyone: men and women, young and old. Although more women than men seek treatment for depression, this does not necessarily mean that men are less likely to get depressed. It could mean they are more reluctant to seek help.

Sometimes there is a trigger for depression. Life-changing events, such as bereavement, having a baby or losing your job, can all cause depression. But you can also become depressed for no obvious reason.

What is the difference between feeling low and depression?

Feeling low or down is something we all experience from time to time. It's a common response to sad or difficult events and situations. Depression is when these feelings are persistent or so strong that they prevent you from doing the things you would normally do.

What are the symptoms of depression?

Symptoms of depression include lasting feelings of sadness, losing interest in the things you used to enjoy, feeling constantly tired,

having difficulty getting to sleep, loss of appetite and feeling life is not worth living.

When to seek medical help

The assessment you have completed indicates that you are depressed and should talk to your GP immediately so that you can decide what are the best options to help you deal with this.

If you start feeling like you can't cope, life is becoming very difficult or your life isn't worth living, get help straight away. These are signs that you need to talk to someone.

Either contact your GP or call NHS Direct (0845 4647). You can also contact help lines such as Samaritans (08457 90 90 90) for confidential, non-judgemental emotional support.

What treatment is available for depression?

Depression is mostly treated in primary care. This means that GPs generally help you choose the most appropriate treatment and manage your care. People with depression are now offered a wide range of treatment options including:

Antidepressants

Psychological therapies such as cognitive behavioural therapy (CBT) and counselling.

Guided self-help, which could, for example, mean your GP gives you a list of recommended self-help books.

Advice on changes you can make to your lifestyle that will help you.

“The type of treatment or combination of treatments that suits you will depend on your preferences, your general health and on how severe your depression is,” says Dr Alan Cohen, a GP with a special interest in mental health.

Many people with moderate or severe depression wait a long time before seeking help. Dr Cohen’s advice is to seek help early.

“There is a range of options available to treat depression. With the right treatment most people make a full recovery. The sooner you get help, the sooner you’ll feel better.”

Appendix 14: Information Hand-out for Mild Depression

Movement Disorder Clinic,
Medicine for the Elderly
East Block, Level 3,
Norfolk and Norwich University Hospital
Colney Lane
Norwich. NR4 7UY
Tel: 01603 288173

The use of carer assisted adherence therapy for people with Parkinson's disease and their carers.

Dear

When you completed the Hospital Anxiety and Depression Scale as part of the above titled study, your score indicated that you may be suffering from mild depression. We will send a letter to your GP also giving them this information.

Depression is a common condition. About one in six people will experience depression during their lifetime (NHS Direct 2010).

It can affect anyone: men and women, young and old. Although more women than men seek treatment for depression, this does not necessarily mean that men are less likely to get depressed. It could mean they are more reluctant to seek help.

Sometimes there is a trigger for depression. Life-changing events such as bereavement, having a baby or losing your job, can all cause depression. But you can also become depressed for no obvious reason.

What is the difference between feeling low and depression?

Feeling low or down is something we all experience from time to time. It's a common response to sad or difficult events and situations. Depression is when these feelings are persistent or so strong that they prevent you from doing the things you would normally do.

What are the symptoms of depression?

Symptoms of depression include lasting feelings of sadness, losing interest in the things you used to enjoy, feeling constantly tired, having difficulty getting to sleep, loss of appetite and feeling life is not worth living.

Self help Strategies

Mild depression, in particular, is more likely to respond to self-help. There are several things you can do yourself that might help you cope better with depression or prevent another episode of depression. These include exercising on a regular basis and finding a support group. Sources of good quality self-help information are given at the bottom of this sheet.

If you're still feeling down after a couple of weeks, please talk to your GP or call NHS Direct (0845 4647).

Good Quality Information Sources

NHS Direct

NHS Direct is here to make a difference to the lives of people in England, 24 hours a day, 365 days a year. We're here for you whenever you have health worries and we have the knowledge and experience to give you real help and reassurance.

Tel: 0845 4647

Web:

<http://www.nhs.uk/livewell/depression/pages/depressionhome.aspx>

BBC Health

Web:

http://www.bbc.co.uk/health/emotional_health/mental_health/disorders_depression.shtml

SANE: Mental Health Charity

SANEline and SANEmail offer emotional support and information to those experiencing mental health problems, their families and carers.

Contact **SANEline / SANEmail:**

1st Floor Cityside House, 40 Adler Street, London, E1 1EE

Helpline: 0845 767 8000, fax: 020 7375 2162

email: sanemail@sane.org.uk

web: www.sane.org.uk

Web: <http://www.sane.org.uk/AboutMentalIllness/Depression>

MIND: Mental Health Charity

Mindinfo

We are able to provide information on a range of topics including types of mental distress, where to get help, drug and alternative treatments and advocacy. We are able to provide details of help and support for people in their own area.

Contact Mindinfo:

Mindinfo

PO Box 277

Manchester

M60 3XN

Tel: 0845 766 0163

email: info@mind.org.uk

Web:

http://www.mind.org.uk/help/diagnoses_and_conditions/depression

Appendix 15: Letter to General Practitioner Regarding Patients Depression



Movement Disorder Clinic,
Medicine for the Elderly
East Block, Level 3,
Norfolk and Norwich University Hospital
Colney Lane
Norwich. NR4 7UY
Tel: 01603 288173

Date.....

**The use of carer assisted adherence therapy for people with
Parkinson's disease and their carers: CAAT-PARK**

Dear Dr

When your patient completed the Hospital Anxiety and Depression Scale as part of the carer assisted adherence therapy for patients with Parkinson's disease (CAAT-PARK), their score indicated that they may be suffering from depression.

Your patient's HADS score showed mild moderate/severe depression (*delete as appropriate*) indicated by a score of _____. This was assessed on (*date*)

We informed your patient of this immediately and gave them an information sheet regarding the management of depression in line with NICE Guidance (2009), a copy of which is enclosed with this letter. They are aware that we are contacting you regarding our concerns for their wellbeing.

If you require any further information, please contact Mr David Daley, (Chief Investigator) Tel: 01603 593665, E-mail: david.daley@nnuh.nhs.uk; or Dr Phyo Myint, (Project supervisor), Tel: 01603 286286, E-mail: phyo.myint@nnuh.nhs.uk

Yours sincerely

David Daley
Chief Investigator

Appendix 16: Baseline Demographics Form



DEMOGRAPHICS FORM – CAAT-PARK

Assessment Date: (e.g. 02-Jan-01)

--	--	--

Gende <input type="checkbox"/> Male <input type="checkbox"/> Female	Date of Birth ____/____/____ dd mm yy
Race: <input type="checkbox"/> White British <input type="checkbox"/> Black British <input type="checkbox"/> Indian <input type="checkbox"/> Caucasian <input type="checkbox"/> White/ Black Africa <input type="checkbox"/> Chinese <input type="checkbox"/> Caribbean <input type="checkbox"/> Pakistani <input type="checkbox"/> Bangladeshi <input type="checkbox"/> Other	

MEDICAL HISTORY

Does the subject have a history of or currently have any of the following diseases or conditions?

Condition	No	Yes	Diagnosis or description of abnormality	Date	Continuing ? Yes/no
Allergy (inc drugs)					
HEENT					
Respiratory					
Cardiovascular					
Gastrointestinal					
Genitourinary					
Neurological & psychiatric					
Haematology & Lymphatic					
Endocrine & metabolic					
Dermatological					
Musculoskeletal - Including duration of knee pain					
Surgical History					
Other					

In what year were you diagnosed with Parkinson's disease?

Do you take the medication on your own?

Yes No

Does somebody remind you sometimes to take your medication?

Yes No

What is the first part of your postcode? _ _ _

What is your occupation?

What is your relationship with the person who you have nominated to also receive the adherence therapy?

- | | | |
|---------------------------------------|---|---|
| <input type="checkbox"/> Spouse | <input type="checkbox"/> Child | <input type="checkbox"/> Grandchild |
| <input type="checkbox"/> Neighbour | <input type="checkbox"/> Brother/Sister | <input type="checkbox"/> Other relative |
| <input type="checkbox"/> Paid carer | | |
| <input type="checkbox"/> Other: | | |

Does this individual live with you in your home?

Yes No

Are you currently taking part in any other healthcare research? (*Please tick*)

Yes No

.....
.....
.....

Appendix 17: Hoehn & Yahr Scale of Parkinson's disease Severity

- 0: Asymptomatic.
- 1: Unilateral involvement only.
- 2: Bilateral involvement without impairment of balance.
- 3: Mild to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.
- 4: Severe disability; still able to walk or stand unassisted.
- 5: Wheelchair bound or bedridden unless aided.

Appendix 18: UK Parkinson's disease Brain Bank Clinical Diagnostic Criteria

Step 1. Diagnosis of Parkinsonian Syndrome:

- Bradykinesia
- At least one of the following
 - o Muscular rigidity
 - o 4-6 Hz rest tremor
 - o 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 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- presence of cerebral tumor or communication hydrocephalus on imaging study
- negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3 supportive prospective positive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease in combination with step one:

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

Appendix 19: Letter of Invitation



Movement Disorder Clinic,
Medicine for the Elderly
East Block, Level 3,
Norfolk and Norwich University Hospital
Colney Lane
Norwich. NR4 7UY
Tel: 01603 288173

Date.....

Dear

We would like to invite you to take part in a research study which is being conducted by Ph.D student Mr David Daley, who will act as Chief Investigator for this project. You have been identified by the clinical team at Norfolk and Norwich University Hospital because you are due to attend an out-patient appointment within the next few weeks for your Parkinson's disease. David is working under the supervision of three academic supervisors: Dr Phyoo Myint, Dr Katherine Deane, and Professor Richard Gray. The study title is:

The use of carer assisted adherence therapy for people with Parkinson's disease and their carers.

Enclosed with this letter you will find:

A participant information sheet detailing the exact nature and purpose of the study,
The Morisky Medication Adherence Scale,
A consent form for the Morisky Medication Adherence Scale,
An envelope entitled 'Carer Information'.

We know that sometimes people are not always able to take their medications exactly as prescribed, and we call this 'poor adherence'. We understand this can be for a variety of reasons. The aim of this study is to find out if a programme of carer assisted adherence therapy helps people who have Parkinson's disease to take their medication as prescribed.

We are looking to get people who have difficulty sticking with taking their pills. The Morisky Medication Adherence Scale will

allow us to see if you have this problem. If you do you will be invited to take part in the full study. We will phone you to inform you of this before your out-patient appointment. If the Morisky Medication Adherence Scale shows you don't have this problem, again we will inform you of this by phone but we won't need you to take part.

We are also looking to recruit spouses or other adults who may help you to take your medication. If there is someone you think might be interested in joining this study, please give them the enclosed envelope entitled 'Carer Information'.

You do not have to take part in this study and you can withdraw from it at any time without giving an explanation. This will not affect the standard of care given to you.

Please take the time to read carefully the participant information sheet enclosed before deciding if you would like to take part. The participant information sheet will tell you what to do next.

Yours Sincerely

Consultant Physician
Medicine for the Elderly

If you require any further information, please contact:

Mr David Daley (Chief Investigator),
Tel: **01603 593665**, Monday to Friday, Office hours.

Dr Phyo Myint (Study Supervisor),
Honorary Consultant in Stroke Medicine, Norfolk & Norwich
University Hospital NHS Foundation Trust
Tel: **01603 286286**, Monday to Friday, Office hours.

Appendix 20: Patient Information Sheet

Invitation to participate in a research study

We would like to invite you to take part in a research study. The study title is:

The use of carer assisted adherence therapy for people with Parkinson's disease and their carers

Before you decide whether to participate you need to understand why the research is being conducted and what it will involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Please ask us if there is anything that is not clear. Our contact details are given at the end of this leaflet.

What is the purpose of the Study?

The most effective treatment for people with Parkinson's disease is medication. We know that many people with Parkinson's do not always stick to their exact medication schedules correctly. This can be for several reasons. We call this 'poor adherence'.

Sometimes healthcare professionals don't know which way of helping people take their medications is best. To find out, we need to test new methods.

The aim of this study will be to determine if a treatment called 'carer assisted adherence therapy' can help people to stick to their medication schedule. To do this we need to compare the new treatment to the normal methods we use - i.e. 'treatment as usual'.

If you are eligible and also willing to participate in the study, you have an equal chance of being in either group. The results are compared to see which treatment is better.

Why have I been invited?

This is because you attend Norfolk and Norwich University Hospital for appointments in Medicine for the Elderly. These appointments are for your Parkinson's disease for which you are receiving medication.

Do I have to take part?

Participation is entirely voluntary. It is up to you to decide. We will describe the study in this information leaflet. We will then go through it with you when you attend your hospital appointment which is in a few weeks time. If after this you decide you would like to take part in the full study, we will ask you to sign a consent form to show you have agreed. You are free to withdraw at any time, without giving a reason. This would not affect the care you receive.

What will be involved if I take part?

Stage 1:

If you think you might like to take part, we would like you to complete the 'Morisky Medication Assessment Scale' enclosed. We would also like you to complete and sign the consent form that accompanies this scale. **You are NOT consenting to the full study by signing this consent form.** This consent form simply states that you are happy to complete the scale. We would then like you to return the consent form and the scale to David (who is working for his Doctorate degree with this project) in the pre-paid envelope provided. We would be grateful if you would do this as soon as is convenient for you.

Stage 2:

After receiving the Morisky Medication Assessment Scale and the consent form from you, a member of the clinical team will phone before your outpatient appointment for your Parkinson's disease. If you are **NOT** eligible for the study you will be thanked for returning the scale, however, you will not be needed for the full study. If you **ARE** eligible for the full study, the clinical team will phone to tell you this. David would then like to discuss the study in further detail after your outpatient appointment with your nurse specialist or doctor. Please allow for one hour extra after your appointment so that David can provide you with all of the information and answer any questions you may have.

We are also very interested in your spouse/ carer participating with you. If your spouse/ carer is interested in taking part also, it would be helpful if they could attend clinic with you to talk about the study.

As the new treatment requires visiting you in your own home, we would ask you to **bring your diary** if possible to your outpatient appointment for your Parkinson's disease. If you are assigned to the

‘carer assisted adherence therapy’ group, David would like to book some dates with you for the first few sessions.

At your appointment you will see the nurse/ doctor as you usually would. You will be asked by them if you are still interested in taking part. If you have changed your mind, you do **NOT** have to speak with David. If you would like to take part, or you are not sure and would like more information first, the nurse/ doctor will ask you to speak with David after the appointment. Please note this is only if you want to.

David will go through the study information and answer any questions or concerns you may have. Once you have a good understanding you can then decide whether to take part. If you are happy to carry on you will be asked to sign the consent form for the full study.

All Study Participants:

After consenting some initial assessments will be made. These are painless and consist of mostly questions. This process will take about 30 minutes. You are free to withdraw at anytime should you wish.

Stage 3:

After answering the questions, David will allocate you to either the ‘carer assisted adherence therapy’ group **OR** the ‘treatment as usual’ group. This will be done entirely at random and you have **an equal chance** of being in either group.

‘Treatment as Usual’:

If you are assigned to the ‘**treatment as usual**’ group you will be asked to complete some more questionnaires at home and return them in the pre-paid envelope. We will ask you to complete the same questionnaires again 7 weeks after seeing David in clinic and once more 4 weeks after this. Other than this, your care will be the same as normal.

‘Carer Assisted Adherence Therapy’:

Adherence therapy is a treatment that is given once per week by David. The therapy lasts for 7 weeks. If you need to miss a week, this is ok. But it would then mean that your therapy would need to be carried over into an eighth week. Each weekly session will be conducted in your **own home** and will last 20 minutes. The therapy requires you to discuss with David your feelings about your medicines.

If you are assigned to the ‘carer assisted adherence therapy’ group you will also be asked to complete some questionnaires at home and return them in the pre-paid envelope. We will ask you to complete the same questionnaires immediately after completing the ‘carer assisted adherence therapy’ programme and once more about one month later. This time point will represent exactly twelve weeks from the day you first saw David in clinic.

As this treatment is ‘carer assisted adherence therapy’, we hope this can be given to you **AND** a carer. This is somebody you nominate who may help you with taking, or reminding you to take, your medicines. This person can be your spouse or a friend, relative or formal carer. You are still able to take part without a carer if you wish. The carer would be asked to sit in on the seven sessions with you. If you have somebody who you might like to take part with you, please give them the enclosed envelope entitled ‘carer information’.

On rare occasions David may ask if he can audio-record one of the sessions. This is so we can ensure the sessions are running as planned. The audio-recording will not be used for any other purpose. You can say no to David audio-recording the session if you wish. Once it has been verified by the research team that the sessions are running as planned, the audio-recording will be deleted.

Ten people with Parkinson’s disease and their carers will also be asked, towards the end of the study, if they would like to participate in a more detailed interview with David. This will be to investigate in more depth their views on the adherence therapy process. If you are chosen to be one of these people we will give you some further information and a consent form. As before, there is **NO** obligation on you to participate and your care will not be affected.

Expenses and payment

Although we do not have available funding to compensate you for your time, additional car park expenses incurred while you are with David after your outpatient appointment will be reimbursed to you.

What are the risks of me taking part?

We do not predict any risks or distress directly resulting from the ‘carer assisted adherence therapy’. However, if you feel distressed as a result of talking to David about your medicines, you can contact Dr

Phyo Myint on 01603 286286 (Consultant Physician), David's supervisor, who will assist you appropriately.

What is the benefit of me taking part?

We cannot promise that the findings of this study will directly benefit you, but the information we get from this study will be used to help improve treatments for people with Parkinson's disease.

What will happen if I don't want to carry on with the study?

If you decide you no longer wish to participate you can withdraw at anytime, without giving a reason. Withdrawal from the study will not affect your usual care. If you are in the 'treatment as usual' group and withdraw, you will then receive treatment as usual but without completing any further questionnaires. We will need to keep the data collected up to your withdrawal.

If you are in the 'carer assisted adherence therapy' group and withdraw, you will then just receive treatment as usual. You could stop receiving the therapy sessions but still complete all questionnaires. Or you could withdraw completely from the study. Again, we will need to keep the data collected up to your withdrawal.

What if there is a problem?

Any complaint about the way you have been dealt with during the study will be addressed. If you have any concerns about the study, you can talk directly to the researchers. It is not expected that you will suffer any harm from taking part in this study. However, any grievances can be directed to the researchers, the complaints office, or the Patient Advice and Liaison Service (PALS). You can find more contact details on the internet at <http://www.pals.nhs.uk> or by contacting PALS at the Norfolk and Norwich University Hospital.

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will be happy to help you. Their contact details are:

Mr David Daley (Chief Investigator) Tel: 01603 593665, Monday to Friday, Office hours, E-mail: david.daley@nnuh.nhs.uk

Dr Phyo Myint (Project Supervisor), Medicine for the Elderly department, Tel: 01603 286286, Monday to Friday, Office hours

Will my taking part be kept confidential?

Yes. All information which is collected about you during the study will be kept strictly confidential and stored in line with the Data Protection Act (1998). Only investigators from our team (who have formal legal duties of confidentiality) will have access to this information.

We will give you a number when you join the study and this number will be used on all the documents instead of your name so you cannot be identified. With your agreement, we will write to your GP to tell them you are taking part in this study.

Data from this research will be stored securely for up to five years after the study is completed to allow us to fully analyse all of the data. After this time the data will be disposed of securely.

What will happen to the results of the study?

The results of the study will be used as part of a written Ph.D thesis which will be submitted to the University of East Anglia. The results of the study will also be published in a research paper. A report will be sent to Parkinson's UK. In all situations you will not be identifiable.

Yes, I would like to take part – what do I need to do now?

Please complete and return in the pre-paid envelope the Morisky Medication Assessment Scale and the accompanying consent form for the scale. If you need help with the consent form or scale, please phone us and we will be happy to help. Once you have returned the two documents in the post, a member of the clinical team will phone you to thank you for this. They will also inform you as to whether you are eligible for the full study.

Who is organising and sponsoring the study?

This study is part of a three year Ph.D studentship project funded by the University of East Anglia. The Chief Investigator is Ph.D student, Mr David Daley. David will work under the supervision of Dr Phyo Myint, Dr Katherine Deane and Professor Richard Gray.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee. This is to protect your safety, rights, wellbeing and dignity. The study has been reviewed,

and given a favourable opinion, by Cambridge Central NHS Research Ethics Committee. This study has also been approved by Norfolk and Norwich University Hospital Research and Development.

Thank you for reading this information sheet

**If you require further information please contact
David on: 01603 593665, Monday – Friday, office hours.**

A friend or relative may speak to us on your behalf if you wish.

**Alternatively you could contact Dr Phyo Myint on: 01603
286286.**

We will be happy to answer any questions or concerns you

Appendix 21: Consent Form for Morisky Medication Adherence Scale



Movement Disorder Clinic,
Medicine for the Elderly
East Block, Level 3,
Norfolk and Norwich University Hospital
Colney Lane
Norwich. NR4 7UY
Tel: 01603 288173

Date.....

Assigned Clinic Number:

The use of carer assisted adherence therapy for people with Parkinson’s disease and their carers.

(Please initial box)

I confirm that I have read and understood the participant information sheet dated 01/06/11 (version 2.0) for the above study.

I have had the opportunity to consider the information and ask questions.

I agree to completing the Morisky Medication Adherence Scale (MMAS).

I agree to a member of the clinical team contacting me by Phone to inform me of whether I am eligible to take part in the full study.

Participant’s Name
.....

Participant’s Signature
.....

Date
.....

Appendix 22: Carer Information Sheet

Invitation to participate in a research study

We would like to invite you to take part in a research study. The study title is:

The use of carer assisted adherence therapy for people with Parkinson's disease and their carers

Before you decide whether to participate you need to understand why the research is being conducted and what it will involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Please ask us if there is anything that is not clear. Our contact details are given at the end of this leaflet.

What is the purpose of the Study?

The most effective treatment for people with Parkinson's disease is medication. We know that many people with Parkinson's do not always stick to their exact medication schedules correctly. This can be for several reasons. We call this 'poor adherence'.

Sometimes healthcare professionals don't know which way of helping people take their medications is best. To find out, we need to test new methods.

The aim of this study will be to determine if a treatment called '**carer assisted adherence therapy**' can help people to stick to their medication schedule. To do this we need to compare the new treatment to the normal methods we use - i.e. '**treatment as usual**'. If your spouse/ carer is eligible and wants to participate in the study, together you have an equal chance of being in either group. The results are compared to see which treatment is better.

Why have I been invited?

This is because you are the spouse/ carer of a person who attends Norfolk and Norwich University Hospital for appointments in Medicine for the Elderly. These appointments are for your spouse's/ relative's Parkinson's disease for which they are receiving medication.

Do I have to take part?

Participation is entirely voluntary. It is up to you to decide. We will describe the study in this information leaflet. We will then go through it with you if you accompany your spouse/ relative to their hospital appointment in a few weeks time. This appointment is for their Parkinson's disease. If you could accompany your spouse/ relative to their appointment, this would be very helpful. If after this you decide you would like to take part in the full study, we will ask you to sign a consent form to show you have agreed. You are free to withdraw at any time, without giving a reason. This would not affect the care your spouse/ relative receives.

If you are not able to accompany your spouse/ relative to their appointment for their Parkinson's disease, but you think you might like to participate, we will give your spouse/ relative some more information (including a consent form) which they can give to you. We would ask if you could please return these in the provided pre-paid envelope as soon as is convenient.

What will be involved if I take part?

Stage 1:

Your spouse/ relative have been provided with some information about this study. If they think they might like to take part, we have asked them to return a short questionnaire (the Morisky Medication Adherence Scale) and a consent form for this questionnaire, to David (who is working for his Doctorate degree with this project). **They are NOT consenting to the full study by signing this consent form.** This questionnaire is designed to identify anybody who may from time to time not take their medication exactly according to their prescribed schedule. These are the people we would like to take part in the study.

Stage 2:

After receiving the Morisky Medication Adherence Scale and the consent form from your spouse/ relative, a member of the clinical team will phone before their outpatient appointment for their Parkinson's disease. If your spouse/ relative is **NOT** eligible for the study they will be thanked for returning the scale, however, they will not be needed for the full study.

If your spouse/ relative **IS** eligible for the full study, the clinical team will phone to tell them this. David would then like to discuss the study in further detail after their outpatient appointment with the nurse specialist or doctor. Please allow for one hour extra after the

appointment so that David can provide you both with all of the information and answer any questions you may have.

As the new treatment requires visiting your spouse/ relative in their own home, we would ask you both to **bring your diary** if possible to the outpatient appointment. If you are assigned to the 'carer assisted adherence therapy' group, David would like to book some dates with you for the first few sessions.

At your spouse's/ relative's appointment they will see the nurse/ doctor as they usually would. They will be asked if they are still interested in taking part. If they or you have changed your mind, you do **NOT** have to speak with David. If you would like to take part, or you are not sure and would like more information first, the nurse/ doctor will ask you to speak with David after the appointment. Please note this is only if you want to.

David will go through the study information and answer any questions or concerns you may have. Once you have a good understanding you can then decide whether to take part. If you are happy to carry on you will be asked to sign the consent form for the full study.

All Study Participants:

After consenting some initial assessments will be made. These are painless and consist of mostly questions. One of the questionnaires we will ask you to complete will be different to the ones your spouse/ relative complete. This process will take about 30 minutes. You are free to withdraw at anytime should you wish.

Stage 3:

After answering the questions, David will allocate your spouse/ relative to either the 'carer assisted adherence therapy' group **OR** the 'treatment as usual' group. This will be done entirely at random and they have **an equal chance** of being in either group.

'Treatment as Usual':

If your spouse/ relative is assigned to the '**treatment as usual**' group they will be asked to complete some more questionnaires at home and return them in the pre-paid envelope. You will be asked to do this too. We will ask you both to complete the same questionnaires again 7 weeks after seeing David in clinic and once more 5 weeks after this. Other than this, your spouse's/ relative's care will be the same as normal.

‘Carer Assisted Adherence Therapy’:

Adherence therapy is a treatment that is given once per week by David. The therapy lasts for 7 weeks. If your spouse/ relative needs to miss a week, this is ok. But it would then mean that the therapy would need to be carried over into an eighth week. Each weekly session will be conducted in your spouse’s/ relative’s **own home** and will last 20 minutes. The therapy requires both you and your spouse/ relative to discuss with David your feelings about the Parkinson’s medicines.

If your spouse/ relative is assigned to the ‘**carer assisted adherence therapy**’ group you will also be asked to complete some questionnaires at home and return them in the pre-paid envelope. We will ask you to complete the same questionnaires immediately after completing the therapy sessions and once more 5 weeks after this.

On rare occasions, David may ask if he can audio-record one of the sessions. This is so we can ensure the sessions are running as planned. The recording will not be used for any other purpose.

Ten people with Parkinson’s disease and their carers will also be asked, towards the end of the study, if they would like to participate in a more detailed interview with David. This will be to investigate in more depth their views on the adherence therapy process. If you are chosen to be one of these people we will give you some further information and a consent form. As before, there is **NO** obligation on you to participate and your spouse’s/ relative’s care will not be affected.

Expenses and payment

Although we do not have available funding to compensate you for your time, additional car park expenses incurred while you are with David after the outpatient appointment will be reimbursed to you.

What are the risks of me taking part?

We do not predict any risks directly resulting from the ‘carer assisted adherence therapy’.

What is the benefit of me taking part?

We cannot promise that the findings of this study will directly benefit you, but the information we get from this study will be used to help improve treatments for people with Parkinson's disease.

What will happen if I don't want to carry on with the study?

If you decide you no longer wish to participate you can withdraw at anytime, without giving a reason. Withdrawal from the study will not affect your spouse's/ relative's usual care. If you are in the 'treatment as usual' group and withdraw, you will then receive treatment as usual but without completing any further questionnaires. We will need to keep the data collected up to your withdrawal.

If you are in the 'carer assisted adherence therapy' group and withdraw, you will then just receive treatment as usual. You could stop receiving the therapy sessions but still complete all questionnaires. Or you could withdraw completely from the study. Again, we will need to keep the data collected up to your withdrawal. If you withdraw, your spouse/ relative can continue to participate.

What if there is a problem?

Any complaint about the way you have been dealt with during the study will be addressed. If you have any concerns about the study, you can talk directly to the researchers. It is not expected that you will suffer any harm from taking part in this study. However, any grievances can be directed to the researchers, the complaints office, or the Patient Advice and Liaison Service (PALS). You can find more contact details on the internet at <http://www.pals.nhs.uk> or by contacting PALS at the Norfolk and Norwich University Hospital.

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will be happy to help you. Their contact details are:

Mr David Daley (Chief Investigator) Tel: 01603 593665, Monday to Friday, Office hours, E-mail: david.daley@nnuh.nhs.uk

Dr Phyo Myint (Project Supervisor) Tel: 01603 286286, Monday to Friday, Office hours

Will my taking part be kept confidential?

Yes. All information which is collected about you during the study will be kept strictly confidential and stored in line with the Data Protection Act (1998). Only investigators from our team (who have formal legal duties of confidentiality) will have access to this information.

We will give you a number when you join the study and this number will be used on all the documents instead of your name so you cannot be identified. Data from this research will be stored securely for up to five years after the study is completed to allow us to fully analyse all of the data. After this time the data will be disposed of securely.

What will happen to the results of the study?

The results of the study will be used as part of a written Ph.D thesis which will be submitted to the University of East Anglia. The results of the study will also be published in a research paper. A report will be sent to Parkinson's UK. In all situations you will not be identifiable.

Yes, I would like to take part – what do I need to do now?

If your spouse/ relative also wish to take part they need to complete and return in the pre-paid envelope the Morisky Medication Assessment Scale and the accompanying consent form for the scale. If they need help with the consent form or scale, please phone us and we will be happy to assist. Once your spouse/ relative have returned the two documents in the post, a member of the clinical team will phone them to thank them for this. They will also inform your spouse/ relative as to whether they are eligible for the full study.

Who is organising and sponsoring the study?

This study is part of a three year Ph.D studentship project funded by the University of East Anglia. The Chief Investigator is Ph.D student, Mr David Daley. David will work under the supervision of Dr Phyo Myint, Dr Katherine Deane and Professor Richard Gray.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee. This is to protect your

safety, rights, wellbeing and dignity. The study has been reviewed, and given a favourable opinion, by Cambridge Central NHS Research Ethics Committee. This study has also been approved by Norfolk and Norwich University Hospital Research and Development.

Appendix 23: Carer Initial Consent Form



Movement Disorder Clinic,
Medicine for the Elderly
East Block, Level 3,
Norfolk and Norwich University Hospital
Colney Lane
Norwich. NR4 7UY
Tel: 01603 288173

Date.....

Assigned Clinic Number:

The use of carer assisted adherence therapy for people with Parkinson's disease and their carers.

(Please initial box)

I confirm that I have read and understood the participant information sheet dated 11/04/11 (version 1.0) for the above titled study.

I have had the opportunity to consider the information and ask questions.

I understand that my participation is voluntary and that I can withdraw at any time without my spouse's/relative's medical care or legal rights being affected.

I understand that my collected data may be looked at by authorised individuals at the University of East Anglia, however, this would be anonymous.

I agree to my sessions potentially being audio recorded. Permission for this will be sought by David (Chief Investigator) at the time.

I agree to take part in the research study.

Participant's Name

.....

Participant's Signature

.....

Date

.....

Chief Investigator's Name

.....

Chief Investigator's Signature

.....

Date

.....

Appendix 24: Patient Informed Consent Form



Movement Disorder Clinic,
Medicine for the Elderly
East Block, Level 3,
Norfolk and Norwich University Hospital
Colney Lane
Norwich. NR4 7UY
Tel: 01603 288173

Date.....

Assigned Clinic Number:

CRTU randomisation Number:

The use of carer assisted adherence therapy for people with Parkinson's disease and their carers.

(Please initial box)

I confirm that I have read and understood the participant information sheet dated 01/06/11 (version 2.0) for the above titled study.

I have had the opportunity to consider the information and ask questions.

I understand that my participation is voluntary and that I can withdraw at any time without my medical care or legal rights being affected.

I understand that my collected data may be looked at by authorised individuals at the University of East Anglia, however, this would be anonymous.

I agree to my GP being informed of my participation.

I agree to my sessions potentially being audio recorded. Permission for this will be sought by David (Chief Investigator) at the time.

I agree to take part in the research study.

Participant's Name

.....

Participant's Signature

.....

Date

.....

Chief Investigator's Name

.....

Chief Investigator's Signature

.....

Date

.....

Appendix 25: Carer Informed Consent Form



Movement Disorder Clinic,
Medicine for the Elderly
East Block, Level 3,
Norfolk and Norwich University Hospital
Colney Lane
Norwich. NR4 7UY
Tel: 01603 288173

Date.....

Assigned Clinic Number:

The use of carer assisted adherence therapy for people with Parkinson's disease and their carers.

(Please initial box)

I confirm that I have read and understood the participant information sheet dated 01/06/11 (version 1.0) for the above titled study.

I have had the opportunity to consider the information and ask questions.

I understand that my participation is voluntary and that I can withdraw at any time without my spouse's/relative's medical care or legal rights being affected.

I understand that my collected data may be looked at by authorised individuals at the University of East Anglia, however, this would be anonymous.

I agree to my sessions potentially being audio recorded. Permission for this will be sought by David (Chief Investigator) at the time.

I agree to take part in the research study.

Participant's Name

.....

Participant's Signature

.....

Date

.....

Chief Investigator's Name

.....

Chief Investigator's Signature

.....

Date

.....

Appendix 26: Adverse Events Checklist



Adverse Events Checklist for Participants in the CAAT Trial Arm

Participant Identification Number:

Date:

Week of Trial:

Number of CAAT sessions received:

Dose: Medication profile:

The following adverse events and drug side effects should be monitored throughout the duration of the CAAT-PARK trial.

Where a study participant is reporting the sudden development or sudden worsening of the below events, this should be reported back to the clinical team immediately for appropriate action to be taken.

Potential Adverse Events to Parkinsonian Medication:

- Falls since the last visit
- Increased nausea to usual level
- Worsening hallucinations
- Sleep disturbances
- Sudden onset of memory loss
- Excessive drowsiness
- Feeling faint or dizzy
- Loss of appetite
- Flu-like symptoms
- Headaches
- behaviour

Number:

- Dyskinesia above usual
- Increased 'OFF' periods
- Worsening tremor
- Increased heart rate
- Change in mood
- Indigestion/constipation
- Flushing/sweating
- Blurred vision
- Uncharacteristic

Comments/Observations:

Appendix 27: Trial Steering Committee Members and Terms of Reference

Trial Steering Committee

Carer Assisted Adherence Therapy for People with Parkinson's disease
(CAAR-PARK) Trial Steering Group

Members:

Dr M Pfeil (Chair)

Mr D Daley (PhD student and study Chief Investigator)

Dr P K Myint (Primary supervisor to PhD student)

Dr K Deane (Supervisor to student)

Prof R Gray (Supervisor to student)

Dr A Clark (Project Medical Statistician)

Dr P Worth (Consultant Neurologist)

Dr K Sabanathan (Consultant Physician in Medicine for the Elderly)

F Reading (Nurse Specialist)

Mr G Ravenhill (Parkinson's disease patient representative)

Mr P Harrison (Parkinson's disease patient representative)

The Committee shall:

Monitor recruitment rates throughout the duration of the trial,

Monitor adverse events and decide upon appropriate action,

Meet every 3-4 months to review the progress of the trial.

Appendix 28: Protocol Submitted to Cambridge Central REC



Study Title: The use of carer assisted adherence therapy for people with Parkinson's disease and their carers: a randomised controlled trial.
Short title: CAAT-PARK

Authors: David James Daley¹, Phyo Kyaw Myint^{1,2}, Katherine Deane¹, Richard Gray¹, Allan Clark¹

¹ Faculty of Medicine and Health Sciences, University of East Anglia, UK

² Norfolk & Norwich University Hospital NHS Foundation Trust

Ethics Ref:

ISRCTN Number: 07830951

3 Background

3.1 Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disease that causes severe disability. Substantial evidence demonstrates that the condition significantly reduces quality of life (QOL) (Lawrence et al., 2003, NICE, 2006, Findley, 2007). The onset of PD can be insidious, and people classically present with cardinal signs and symptoms associated with Parkinsonism: resting tremor, rigidity, bradykinesia (slowness of movement), and hypokinesia (poverty of movement) (Albanese, 2003). Severe symptoms such as postural instability and freezing during mobilisation are characteristically prominent features of advanced stages of disease (Albanese, 2003, Schapira and Obeso, 2006, Jankovic, 2008). Controlling motor symptoms is, therefore, imperative for managing the condition and to ensure optimal QOL for people with PD.

3.1.1 Non-motor symptoms

An extensive body of literature reveals non-motor symptoms significantly debilitate people with PD and further reduce QOL (Hou and Lai, 2007, Poewe, 2008, Löhle et al., 2009, Park and Stacy, 2009). As many as 90% of people with the disease are reported to experience non-motor manifestations throughout the disease process (Shulman et al., 2001). Symptoms include neuropsychiatric problems like depression and hallucinations, sleep disorders, sensory symptoms such as pain and fatigue, and autonomic complaints including hypotension, gastrointestinal problems and urinary system disturbances. As non-motor symptoms become increasing troublesome - often observed in advanced stages of PD - multiple medications are often added (Hou and Lai, 2007). These are in addition to drugs aimed at treating motor symptoms, and, therefore, increase medication regimen complexity.

3.1.2 Cognitive Aspects in PD

Cognitive impairment is estimated to affect between 20-40% of PD patients. Such deficits include reduced frontal lobe executive function, dysfunctional

planning and organisation, visuospatial difficulties, and impaired memory recall and retrieval (Dubois and Pillon, 1997, Hou and Lai, 2007). Even in early disease, subtle decline in cognitive function can be observed (Park and Stacy, 2009). As the disease progresses cognitive decline persists, and PD patients may develop dementia. A meta-analysis of prevalence studies found that rate of dementia is approximately 31% in people with PD (Aarsland et al., 2005).

3.1.3 Prevalence and Healthcare Cost

PD is the second most prevalent neurodegenerative condition after Alzheimer's disease (Mayeux, 1995, Bower, 1999, Nussbaum & Ellis, 2003, Findley, 2007, Schapira et al., 2009). The National Parkinson Foundation (NPF) report that PD affects between 1 and 1.5 million people in the United States (US) and an estimated four to six million worldwide (Oberdorf & Schmidt, 2010). Prevalence rates in the United Kingdom (UK) - as reported by Parkinson's United Kingdom (Parkinson's UK, 2010) - suggest 1 in 500 people within the general population are diagnosed with the condition, equating to 120,000 people nationwide. The prevalence of PD varies with age, with the condition usually affecting older people (Findley, 2007). The incidence of the disease rises with increasing age: one in seven are diagnosed before the age of 50 years (Findley, 2007) with a fivefold increase in PD diagnosis in those over 65 years of age compared to the general population (Schrag et al., 2000, Péchevis et al., 2005).

The prevalence of the disease is forecast to increase substantially in the future due to ageing populations globally. In the UK, this will result in further financial burden on the National Health Service (NHS). Findley (2007) used data from a cross-sectional, survey-based study (Findley et al., 2003) to evaluate the total economic impact of PD on healthcare providers in the UK. Findings showed an estimated total cost of care for PD patients of approximately £450 million - using the most conservative scenario. With a prevalence of 100,000 or greater - as advocated by Parkinson's UK - cost for healthcare analysis shows expenditure to reach as high as £3.3 billion annually (Findley, 2007). In the United States (US), costs for care are estimated to be close to \$23 billion per annum and projected to increase further to as much as \$50 billion by 2040 (Oberdorf & Schmidt, 2010).

3.2 Diagnostic Difficulties with PD

PD represents just one of several Parkinsonian syndromes, making accurate diagnosis a complex pursuit (Albanese, 2003). The most commonly used diagnostic criteria for PD - the reported gold standard - has been proposed by the UK PD Brain Bank (Hughes et al., 1992). These criterion require the use of exclusion criteria and consideration of a parkinsonian syndrome other than PD before a diagnosis of Idiopathic PD can be affirmed (Albanese, 2003). The complexity associated with PD diagnosis is well acknowledged, with definitive diagnosis only possible from autopsy (Hughes et al., 1992). Treating physicians reach a suspected diagnosis of PD using clinical criteria: asymmetric onset, bradykinetic syndrome, cog wheel rigidity, resting tremor, and beneficial response to dopaminergic therapy. However, this may be unclear, especially in the early stages of the disease where symptoms may not

show a clear response to anti-parkinsonian agents. Thus a diagnosis of PD according to UK Brain Bank criteria may take substantial time before all the criteria are achieved and a formal diagnosis of PD is made. In the intervening period clinicians work on a presumptive diagnosis of PD for therapeutic decisions but re-evaluate this assessment for diagnosis at regular intervals.

3.3 Treatment of Parkinson's disease

Levodopa is the gold-standard of anti-parkinsonian medication, representing the mainstay of modern dopaminergic management (Schapira et al., 2009). Prescribed globally, this drug aims to replenish dopamine deficiencies in the Striatum, leading to increased QOL and greater overall life expectancy (Karlsen et al., 2000, Rajput et al., 2001, Schapira et al., 2009).

3.3.1 Medication in Early Disease

Following diagnosis of PD careful consideration is required to establish the optimal dose of medication for a given patient. Traditionally, this has awaited the manifestation of significant motor symptoms and reduced QOL (Schapira et al., 2009). However, evidence is now emerging that suggests early dopamine replenishing therapies offer long-term benefit to patients (Schapira and Obeso, 2006). Furthermore, it is reported that the rate of clinical deterioration is rapid within the first year post diagnosis of PD, with a significant decline of 8-10 points in the Unified Parkinson's Disease Rating Scale - the reported gold standard measure - observed in this short duration (Shults et al., 2002, Fahn et al., 2004). These findings, therefore, support the use of early interventions with anti-parkinsonian therapies from the time of diagnosis.

During early disease the medication profile is typically relatively simple, with just one dopaminergic medication prescribed three times a day. Initially prescribing physicians commence therapy with dopamine receptor agonists, with Levodopa subsequently required as the disease progresses. As advocated by NICE (2006), Levodopa dosage should be kept as low as possible to maintain good function and reduce the development of motor complications.

3.3.2 Medication in Later Disease

As PD progresses, many patients require therapies from various drug classes: Levodopa preparations, Monoamine-oxidase-B inhibitors, Catechol-*O*-methyltransferase inhibitors and dopamine receptor agonists. In the later disease stage modified-release Levodopa preparations may be used to reduce motor complications. Often such drugs regimens are given in addition to other adjuvant anti-parkinsonian medications. As disease progresses and symptoms become increasingly disabling, patients may require intricate titrations and more frequent time specific dosing (Bainbridge and Ruscin, 2009). Moreover, dyskinesias resulting from long-term Levodopa use require additional medications. These often are prescribed with the aim of reducing Levodopa induced motor complications, thus improving QOL (NICE, 2006). However, this addition of supplementary agents leads to further regimen complexity in a population already potentially highly medicated.

In the later disease stage, PD symptoms may be accompanied by comorbidities. Symptoms may include those associated with PD (cognitive

impairment, depression, psychosis) and those relating to general older age. Each of these may increase the number of medications taken, once again adding further to the complexity of drug regimens.

3.4 Medication Adherence in PD

As with many chronic conditions, the effectiveness of prescribed drugs depends not only on the appropriateness and efficacy of the medications given, but additionally on the levels of adherence to the intended therapeutic regimen. Adherence, defined by the World Health Organisation (WHO, 2003) as “*the extent to which a person’s behaviour – taking medication, following diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider*” is of paramount importance for achieving optimal and desirable therapeutic benefit. In PD, pharmaceutical management of the condition can be very helpful in managing motor symptoms and maximising QOL. Consequently, medication adherence in this condition cannot be over emphasised (Rigby, 2007). This is especially pertinent as motor function becomes progressively worse, therefore requiring increasingly intricate medication regimes (Davis et al., 2010).

3.4.1 Prevalence of Non-adherence

A third to half of all medicines prescribed to people with long-term conditions are not taken as recommended (Haynes et al., 2002, WHO, 2003, NICE, 2009). Although it has been recognised that sub-optimal adherence to therapeutic regimens is a major issue in many chronic diseases, it has not long been acknowledged that people with PD may not be consuming their prescribed oral medication as anticipated (Leopold et al., 2004, Grosset, 2010, Grosset et al., 2005, Bainbridge and Ruscin, 2009). One study used electronic medication monitoring caps - which is claimed to be the gold standard assessment method - and questionnaires to show that only 10% of investigated PD patients fully adhered to their prescribed regimen (Leopold et al., 2004). Of these patients, 30% acknowledged missing at least one dose, while 76.4% acknowledged either missed or mistimed doses. Grosset et al (2005) reported 20% of PD patients were under users of their medications. However, these patients and the remaining 80% with reported satisfactory adherence (average total consumption >80%) showed substantial problems with the poor timing of drug doses (number of doses taken at the correct interval). Furthermore, patients were more likely to take their once-daily drugs on time (56% of patients) than drugs that had to be taken more frequently, where only 3% of patients adhered. These findings suggest medication non-adherence is a significant issue in people with PD, and that timed specific dosing is poor, even in people with satisfactory overall adherence.

3.4.2 Non adherence, addiction and motor side effects of drugs

The clinical consequence of non-adherence can be substantial and may lead to inadequate symptom control. This results in significant motor deterioration within a very short duration, leading to reduced QOL (Chaudhuri et al., 2004). The ramifications of poor adherence can be considerably detrimental

to PD patients, especially those in later disease stages where the wearing-off, “on-off” effect, of Levodopa is closely dependent on specific interval dosing. This effect has been postulated to be a consequence of erratic absorption and the short half-life of Levodopa, resulting in fluctuating concentrations. As disease progresses, sporadic dopamine levels in the blood correlate with alternating high and low levels in the brain. This erratic stimulation (peak and trough effect) is displayed as emerging motor fluctuations, causing unwanted reactions to treatment (Bezard et al., 2001). Non-adherence is also an acknowledged factor associated with significantly higher incidence of severe motor related side effects of therapy such as dyskinesias and dystonia (Grosset et al., 2005). These side effects of anti-parkinsonian medications were reported in 100% of early onset PD patients after 6 years of receiving Levodopa (Clarke, 2002).

Non-adherence to medication in PD is not specific to suboptimal intake. Patients may also non-adhere if they over-medicate i.e. Levodopa addiction. Excessive consumption of anti-parkinsonian agents is reported to be prevalent in 10% of patients diagnosed at a younger age (Grosset et al., 2005). The deleterious effects of over-medicating include severe medication induced dyskinesias and potentially the development of significant mental health problems such as psychosis (O’Sullivan et al., 2009).

Inadequate symptom management is not confined to patients living in the community. Unsatisfactory time specific medication consumption is an acknowledged problem in secondary care. Parkinson’s UK has launched their “Get it on time” campaign aiming to ensure people admitted to hospital receive their medications on time, thereby limiting the potential for motor fluctuations. This campaign further emphasises the critical relationship between medication non-adherence and motor deterioration, and helps illuminate the importance of interventions aimed at ensuring patients adhere to their medication dosing as intended.

3.5 Impact of Dyskinesias

Dyskinesias (abnormal involuntary movements) in PD have been linked with significant increases in total health-related costs, with analyses showing an increase in dyskinesia to be associated with an 11% increase in total expenditure. This equates to additional costs of up to £966 per patient over a 6-month period (Pechevis et al., 2005).

Dyskinesias resulting from later stages of disease, and particularly non-adherence to anti-parkinsonian agents have been associated with significant reductions in reported QOL (Pechevis et al., 2005). Furthermore, motor disturbances like bradykinesia and rigidity - unlike tremor and cognitive decline - are sensitive to anti-parkinsonian agents (Bainbridge and Ruscin, 2009). This highlights both the fiscal benefit of limiting motor disturbances through greater medication adherence, and the importance of optimising motor symptom management in order to improve QOL.

3.6 Factors Influencing Adherence in PD

In PD it is not uncommon for patients to be prescribed numerous medications. These often have to be taken at many time points during the day for adequate symptom control. Adherence studies have shown that increasing the number and complexity of medication regimens reduces the rates of adherence in patients with PD. Grosset et al (2005) showed poor adherence was associated with increasing drug complexity. Additionally, this study showed younger age of onset, the presence of depression, and lower reported QOL was also significantly associated with poor adherence to anti-parkinsonian medication. A multicentre study by Grosset and colleagues (2009) showed poor therapy adherence to be associated with poor motor scores, increased periods of “off” time, and worse mobility - measured by a QOL scale.

Cognitive impairment has been significantly associated with non-adherence in people with PD. Furthermore, cognitive impairment has been shown to be even more incapacitating than motor symptoms, especially in more advanced disease (Hou and Lai, 2007, Liepelt et al., 2007). It has been reported that certain demographic variables are positively associated with better adherence. Higher levels of awareness, good knowledge of PD, and living with a spouse have all been shown to offer benefit regarding adherence rates in people with PD (Schlenk et al., 2004, Bainbridge and Ruscin, 2009, Valdeoriola et al., 2010).

In general there are many factors that influence rates of adherence in the elderly population. Age-related factors such as multiple comorbidities can lead to the requirement of an array of medications. In some patients this may result in poor adherence rates (Claxton et al., 2001, Vik et al., 2004). Moreover, individual specific characteristics may contribute further to poor adherence: decreased visual acuity may prohibit identification of correct tablets; reduced dexterity can impede the ability to open bottles or manipulate blister packs. For people with PD, the limitations associated with older age are often intensified by the deleterious impact of PD (Playfer, 2002). Furthermore, forgetfulness is the most common reason for sub-optimal adherence in the general elderly population, with poor memory shown to significantly increase rates of hospitalisation in older adults (Col et al., 1990).

3.7 Carer involvement in the management of PD

For many patients with PD the care they receive - both physically and emotionally - is provided by informal caregivers, such as spouses and other family members (A'Campo et al., 2010). Patients in the early disease stage have low care needs. However, patients with more advanced disease states - especially individuals suffering from cognitive impairment - often require considerable support with daily activities. This may include assisting the person with PD with the management of their medications, i.e. reminding people to take their medications on time, dividing doses into dosette boxes, setting timers, even aiding in the taking of pills with cueing strategies. For the caregiver, the responsibility for timely management of a relative's anti-parkinsonian medication is of grave importance and concern, with many carers left feeling worried and ill-informed (Carers UK, 2010). In PD, where well-timed medication consumption is often paramount for controlling motor

symptoms and limiting ‘off’ periods, carers involved with/ assisting patients with their medications require a full understanding of the importance of sound medication adherence.

3.8 Adherence Guidelines

Both WHO (2003) and NICE (2009) in their adherence guidelines advocate the adoption of an individualised consultation style that recognises patient involvement in treatment decisions as an integral process for facilitating healthcare professionals to enhance rates of adherence. A focus on exploring patients’ beliefs about illness and disease management, in addition to the transference of specific information from professional to patient, are also strongly advocated. Such guidelines have been based on observational research findings, however, there appears to be a paucity of experimental evidence from randomised controlled trials (RCT) supporting the use of such patient centred consultation styles for improving adherence to medication.

3.8.1 Adherence Therapy

Adherence Therapy (AT) is a brief individual cognitive–behavioural approach aimed at facilitating a process of shared decision making where both parties work towards agreed goals (Kemp et al., 1998, Gray et al., 2004). The central theory is that when patients make shared choices with a professional they are more likely to continue with those choices because they are personally owned and meaningful (Gray et al., 2010). The intervention is delivered in six phases that form the core of the therapy: assessment, medication problem-solving, a medication timeline, exploring ambivalence, discussing beliefs and concerns about medication, and using medication in the future (Gray et al., 2006). Key therapy skills that therapists employ incorporate exchanging information, developing discrepancy between the patient’s thoughts and behaviours about medication, and working with resistance to discussing medication and treatment. The aim of the therapy process is to achieve a mutual decision about medication between the individual and therapist. A central ideology of the therapy is that where patients and therapists make choices about treatment mutually, adherence to that regimen will be enhanced (Gray et al., 2006).

3.9 Study Rationale

Non-adherence is a significant problem faced by healthcare professionals attempting to manage the debilitating motor disturbances associated with PD. The reason for medication non-adherence is likely to be multi-factorial. Unfortunately, non-adherence to medication in this population can result in considerably poor symptom management. This leads to a substantially reduced QOL for people with PD. Consequently, it is recognised that there exists a great necessity for methods aimed at improving adherence to prescribed medication. As both common and disabling motor symptoms of bradykinesia and rigidity have been shown to be sensitive to anti-parkinsonian drugs, a targeted therapy is likely to be associated with an overall improved level of medication adherence. This should lead to greater symptom control and hence improve QOL in PD patients with poor adherence.

Interventions aiming to improve adherence to medication have been shown to be effective in enhancing treatment adherence in other chronic mental and physical conditions (e.g. schizophrenia and hypertension) (Kemp et al., 1998, Gray, et al., 2004, Maneesakorn et al., 2007, Staring et al., 2010, Alhalaiqa et al., 2011). However, there is a paucity of research attempting to evaluate and quantify the effects of adherence interventions in people with PD. Furthermore, it is acknowledged that in a complex and multifaceted condition like PD, caregiver involvement in supporting medication adherence can be substantial (Bainbridge and Ruscin, 2009, Valldeoriola et al., 2010). Therefore, carers need to be supported in their role of promoting medication adherence in order to optimise treatment benefit for the individual with PD. To this end, we postulate that an adherence therapy intervention that targets not only people with PD but also their carers is likely to be more beneficial for improving adherence and QOL than an intervention targeted at the person with PD only.

Assuming patients are prescribed correct medication regimens, greater adherence to drugs should result in improved clinical and patient outcomes. Addressing issues surrounding non-adherence in both patients and carers may facilitate optimal disease management and symptom control, ultimately improving health outcomes and QOL. The study will examine the efficacy of an adherence therapy intervention against a control group receiving treatment as usual (TAU) i.e. no intervention believed to impact on adherence.

4 Hypothesis and Study Aims

4.1 Alternate Hypotheses (H_1) – Two-tailed

There will be a statistically significant difference in medication adherence and quality of life in people with PD who undergo a 7 week programme of CAAT in addition to TAU compared to those receiving TAU only.

4.2 Null Hypothesis (N_0)

There will be no statistically significant difference in medication adherence or quality of life in people with PD who undergo a 7 week programme of CAAT in addition to TAU compared to those receiving TAU only.

4.3 Primary Aims:

To investigate if a 7 week programme of CAAT is effective for
improving medication adherence
improving quality of life related to PD
in non-adherent people with PD immediately post intervention and at 12 weeks post randomisation.

4.4 Secondary Aims:

To investigate whether the CAAT and TAU groups differ immediately post intervention and at 12 weeks post randomisation in terms of:

Person with Parkinson's disease:

Overall disease state
Activities of Daily Living
Beliefs about medication
Health related quality of life

Carer of Person with Parkinson's disease:

Beliefs about Medication
Caregiving distress

Treatment Group Only:

To investigate associations between baseline cognitive impairment and efficacy of CAAT.

To investigate associations between baseline anxiety and depression and efficacy of CAAT.

Acceptability/ satisfaction of CAAT for people with PD and their carers.

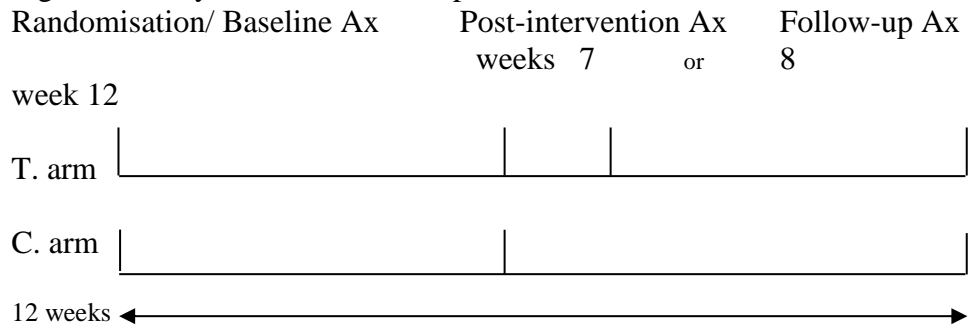
5 Trial Design

5.1 Summary of trial design

This study uses a prospective, block randomised, parallel-group, single-blind design to compare CAAT to TAU for non-adherent people with PD being treated with anti-parkinsonian medications at the Norfolk and Norwich University Hospital (NNUH). Patients attending either routine outpatient movement disorder clinic appointments in Medicine for the Elderly (MFE) or routine appointments in the Neurology department will be randomly allocated to the CAAT or TAU groups, providing informed consent is ascertained and study inclusion criteria are met.

This study will investigate whether CAAT significantly improves levels of adherence and QOL compared to TAU. It will compare the two groups at randomisation (baseline), immediately post intervention, and at 12 weeks post randomisation (follow-up) (Figure one). Participants in the treatment group will be stratified accordingly based on whether they undergo the intervention alone or with a carer. Additionally the study will compare more global outcomes of overall disease state including activities of daily living, beliefs about medication, health related QOL, adherence in relation to levels of anxiety and depression and cognitive impairment. We will also interview a purposive sample of 10 patients and carers to explore experiences and acceptability of the CAAT protocol. The statistical analysis of clinical outcomes will be checked by a blinded statistician. It will not be possible to blind participants or the Chief Investigator (DJD) who will deliver the intervention because of the one-to-one participatory nature of the treatment (patients will know if they are receiving the therapy).

Figure 1: Study Assessment Time points



5.2 Primary and Secondary measurements (Table 1)

Primary outcome measures:

Morisky Medication Assessment Scale (MMAS)

Parkinson's Disease Questionnaire – 39 (PDQ-39)

Secondary outcome measures

Patient Outcomes:

Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) parts 1, 2 and 4 for assessing overall disease state

Activities of Daily Living - measured by the MDS-UPDRS (parts 1 & 2)

Beliefs about Medication Questionnaire (BMQ)

EuroQoL questionnaire (EQ-5D)

Carer Outcomes:

Beliefs about Medicines Questionnaire

Carer Distress Scale (CDS)

Further Data Generation:

Semi-structured interviews of participants' experiences of CAAT (10 people with PD and their carers).

Number of therapy sessions completed (patient and carer) and time taken per session.

The relationship between baseline cognitive impairment (measured by

Montreal Cognitive Assessment Scale (MoCa)) and efficacy of CAAT.

The relationship between baseline anxiety and depression (measured by

Hospital Anxiety and Depression Scale (HADS)) and efficacy of CAAT.

Incidence of adverse events

Table 1: Measurements

Measures	Baseline/ randomisation	Post intervention	Week 12 (follow-up)	Time required for completion
Patient Participants:				
MMAS	x	x	x	2.5 min
PDQ-39	x	x	x	15 min
EQ-5D	x	x	x	2.5 min
BMQ	x	x	x	10 min
Overall MDS- UPDRS score (part 1, 2 and 4)	x	x	x	15 min
MoCa	x			10 min
HADS	x			10 min
Semi- structured interviews *			x	30 min (post-trial)
Satisfaction Questionnaire			x	5 min
Total Time:	65 min	45 min	50 min	
Carer Participants:				
BMQ	x	x	x	10 min
Care Distress Scale	x	x	x	30 min
Semi- structured interview *			x	30 min (post-trial)
Satisfaction Questionnaire			x	5 min
Total Time:	40 min	40 min	45 min	

* Purposively selected sub-sample of 10 patients and carers from CAAT group.

5.3 Trial Participants

The study is aimed at patients who are currently attending Medicine for the Elderly (MFE) or Neurology outpatient appointments at Norfolk and Norwich University Hospital (NNUH) and are being treated with anti-parkinsonian medication for probable or definitive PD. Patients will complete a self-report assessment of their adherence (Morisky Medication Assessment

Scale) and those predicted by this scale to have low adherence (score ≥ 1) will be invited to participate. Carers of patients who provide informed consent and are eligible for the trial will also be invited to participate. Participants randomised into the CAAT group who do not have a carer (formal or informal), or have a carer who does not wish to participate will still be included in the study. Patients who receive AT alone i.e. without carer support will be identified for sub-group analysis.

5.3.1 Inclusion Criteria

Adult patients (18 and over) diagnosed with Idiopathic PD or who have a probable diagnosis of PD (3 out of 4 chief UK Brain Bank criteria are met) i.e. bradykinesia, cog wheel rigidity, resting tremor and postural instability. Prescribed one or more anti-parkinsonian medications by a consultant with specialist knowledge of movement disorders.

English speaking and literate. (We expect the participants to be able to read the information sheet for the CAAT-PARK protocol and fill in a number of self-assessments in English). Less than 1% of the over 50's population in our catchment area are non-English speaking,

Have the required cognitive capacity to read and understand the participant information sheet, consent form and self-report assessments. This will be determined by the clinical team as part of routine out-patient assessment. Show low adherence to anti-parkinsonian therapies as determined by a MMAS score of ≥ 1 .

5.3.2 Exclusion Criteria

Patients who do not have a diagnosis of PD i.e. unable to attribute movement disorders to Parkinson's disease.

Patients with a Parkinsonism's but with no definitive diagnosis of Parkinson's disease e.g. Vascular Parkinsonism, Multiple Systems Atrophy, Progressive Supranuclear Palsy, and Dementia with Lewy body disease.

Patients whose medication regimen has altered within the previous month.

Patients being treated with anti-parkinsonian medications for a mental health issue e.g. psychosis.

Diagnosed with dementia.

Patients with a life expectancy of < 6 months

5.4 Study Procedures

5.4.1 Recruitment

Patients scheduled to be seen in outpatient clinics will be identified by the clinical team and/or Chief Investigator working under supervision of clinical staff two weeks prior to their appointment. The patients' most recent clinic letter will be accessed electronically and used by the clinical team member and/or the Chief Investigator to establish if they meet the inclusion criteria. The Chief Investigator, who holds a valid research passport and Honorary Research Contract with the Trust to facilitate research activity, will post out to patients meeting the inclusion criteria an information pack containing a patient invitation letter signed by the patients consultant (Appendix 12.1), a participant information sheet (PIS) (Appendix 12.2), the MMAS (Appendix 12.3) and a consent form for the MMAS (Appendix 12.4). There will also be

an information sheet and consent form for the spouse/carer (Appendix 12.5 and 12.6). Patients are asked within the information provided to complete and return the MMAS in the pre-paid envelope before their clinic appointment, if they are initially interested in participating. Patients who return the MMAS and its consent form will be contacted by phone by the Chief Investigator to inform them of whether they are eligible to participate or not. Those who are eligible will be informed by the Chief Investigator that he would like to speak with them after their outpatient appointment in a few weeks time. This will allow patients and their spouse/ carer to plan for a slightly longer clinic visit than usual. Those not eligible (i.e. are adherent with their medications) will be thanked for their interest in the study.

Patients who are eligible and consent to participate in the study will be assessed at baseline using measures that require a rater (MoCa, MDS-UPDRS part 1 and 4) by the Chief Investigator after their clinic appointment. The PDQ-39 will also be completed by the participant at this stage to ensure the data is prior to randomisation. It is expected to take 45-60 minutes to explain the study, answer questions, take informed consent and complete baseline assessments. The remaining measures, which are self-assessments, will be given to the participants to complete at home. This allows participants to complete the secondary measures in their own time, hence reducing the time burden associated with their clinic visit. Following the completion of the baseline assessments the Chief Investigator will randomise participants and organise appointment times for the therapy to be delivered at home for participants randomised to the CAAT group. Where there is insufficient time to undertake baseline measures in clinic after clinic appointments, the Chief Investigator will take signed informed consent and then arrange a date to visit the patient in their own home to complete baseline measures. In this instance, patients will be randomised to one of the two treatment arms after baseline assessment and then contacted by phone by the Chief Investigator to inform them of their randomly assigned group.

Consent will be a two stage process: (1) consenting to the MMAS screening tool (posted with the PIS and consent form), (2) consenting to the trial at the time of clinic attendance. Participants will be informed in the PIS that they do not have to consent to the trial until they have had the opportunity to discuss it with the clinical team first, and then the Chief Investigator for further detail if they wish on the day of their clinic appointment. Patients will be made aware in the PIS that the consent form posted to them is only for the MMAS, not the full trial.

5.4.2 Informed Consent for RCT

Clinic nurses/ consultants will briefly discuss the study with patients at the scheduled outpatient appointment. If the patient did not receive the information sheet, they will be sent home with one and not asked to give informed consent on the day. Patients, with or without carers, who have considered the trial prior to their out-patient appointment, are non-adherent based on the returned MMAS, and are expressing an interest in the study to

the clinic nurse/ consultant will be met by the Chief Investigator to discuss the study in further detail.

The Chief Investigator will fully explain the study, the randomisation process, and the requirements of participants in the CAAT and TAU groups in lay language. It will be made very clear from the outset that the patient/ carer is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. The patient will be allowed time to consider the information and ask questions before signing the informed consent form. If further information is required, patients will be encouraged to seek advice from family members, friends or their GP.

Written informed consent will be obtained (Appendix 12.7). This will take place after the scheduled out-patient appointment. A copy of the signed informed consent form will be given to the participant. A copy will be kept with the medical records and the original signed form will be retained by the research team at the University of East Anglia. Patient's General Practitioner (GP) will be informed by letter of their patient's participation in the trial (Appendix 12.8). Consent will be sought for this by means of a tick box on the trial consent form.

Carers who do not attend clinic with the patient, and, therefore, are not able to provide informed consent at the same time, can be consented in the patients' home during the initial visit. Consent from patients' carers may be returned by post to the Chief Investigator if able. Self-assessments which are given to the spouse/ carer, or the patient if they are alone in clinic, can be returned by post to the Chief Investigator in a provided pre-paid envelope. Thirty minutes will be set aside for taking informed consent to ensure patients/ carers possess a sound understanding of the trial. The Chief Investigator will be trained on how to consent patients by the supervisors (PKM, KD), and has received Good Clinical Practice (GCP) training. At each point of participant contact (i.e. visits for delivery of CAAT) ongoing verbal consent will be sought and subjects will be made aware in their PIS of their right to withdraw should they not want to continue (process consent). If patients withdraw they will then receive standard care. Data collected to the point of withdrawal will be retained in the trial data set.

5.4.3 Recruitment and Informed Consent for interviews

Ten patients and carers from the CAAT group will be purposefully sampled to participate in interviews to investigate the acceptability of the CAAT intervention. The purposive sampling frame will draw on priority criteria ensuring diversity in conceptually-relevant characteristics of potential participants, to include: age, sex, cognition and severity of PD. Separate information sheets (Appendix 12.9) and consent forms (Appendix 12.10) will be given to the trial participants at the end of the intervention phase. This will represent a separate consent stage for the interviews. The main information sheet will state that after the trial has been completed, participants may be asked to participate in a half hour interview. It will be clear from the PIS that more information and a separate consent form will be provided at a later date.

The interview specific PIS and consent form will include a relevant section detailing the interview protocol. Participants will be made aware in the information sheet that the interview will need to be audio recorded.

The interview will take place in the patients' homes after the CAAT programme has been completed and all outcome measures and assessments have been documented. Interviews will be undertaken together between the patients and the spouse/ carers unless the participants object and request to undertake a separate interview.

5.4.4 Randomisation

All eligible patients who have provided informed consent to participate in the trial will be randomly assigned to either the CAAT-PARK or TAU arm of the trial. Randomisation will take place at NNUH in a private room after patients have provided consent and have completed the baseline measures (PDQ-39, MDS-UPDRS part 1, MoCa) unless they are randomised following a home visit. In this instance, randomisation will be undertaken by the Chief Investigator from the UEA and the patient will be phoned to inform them of the assigned group.

Once the baseline measures have been undertaken, the Chief Investigator will access the web-based randomisation system, developed by the Clinical Research Trial Unit (CRTU), to randomise the participants. This ensures that the baseline measures are blinded i.e. completed prior to randomisation. Participants will be informed instantly of their group allocation.

Randomisation will be undertaken by the CRTU at the University of East Anglia (UEA). The randomisation schedule will be designed by the trial statistician (Dr Allan Clark, Senior Lecturer in Medical Statistics). The Chief Investigator will be allocated a personal 'PIN' identifier for use when randomising patients and will access a web-based randomisation service set up by CRTU. The system will request the PIN which the Chief Investigator will be required to enter. If access to the internet is unavailable for some reason, the Chief Investigator will phone the trial secretary (Professor Richard Gray's secretary) and they will access the web based randomisation system on the Chief Investigator's behalf.

On entry of a valid PIN, the system will generate a unique study code and randomly allocate the patient to either the CAAT or TAU arm of the trial. The study code and allocation will be reported back on screen and will also be sent in a confirmatory email to a) the Chief Investigator, b) other nominated trial staff and c) the trial database manager. The study code and allocation will be stored in the trial database on the secure CRTU server at UEA. A computer generated randomisation list will allocate patients into either the CAAT or TAU group based on block randomisation (blocks of 4 and 6). Patients randomised into the CAAT arm will be sub-divided into carer or no carer groups respectively.

5.4.5 Baseline characteristics of the trial participants

The following demographic and medical data will be collected at baseline. These will inform assessments of the generalisability of the study, the success of the randomisation process and may help identify potential confounding factors:

People with PD:

Age,
Gender,
Ethnicity,
Duration of diagnosis of PD,
Medication profile (type of medications, dosage level and frequency),
Whether medication is self-administered,
Co-morbidities,
Spouse present in the home,
Occupation,
Socioeconomic status (estimated using first half of participant's postcode),
Level of education,
Current involvement in ongoing research,
Hospital Anxiety and Depression Scale (HADS),
Montreal Cognitive Assessment Scale (MoCA).

Carers:

Age,
Gender,
Ethnicity,
Level of education,
Occupation,
Socioeconomic status (estimated using first half of participant's postcode),
The relationship with the person with PD
Whether they live with the person with PD.

5.4.6 Measurements

Once written informed consent has been obtained, baseline data from participants will be collected (PDQ-39, MDS-UPDRS part 1, MoCa). These will be undertaken in a private consultation room at NNUH. The baseline assessments will be undertaken and patients instructed on how to complete the trial self-report outcome measures.

The remaining baseline secondary outcome measures which are self-reported scales will be given to participants at clinic for completion in their own time. This will reduce any time and fatigue burden that may be associated with the completion of the various outcome measures. Participants will be asked to return the self-report measures within two weeks of receiving them from the Chief Investigator, via a pre-paid envelope. After two weeks the Chief Investigator will contact the participants to remind them to return their baseline forms if they have not yet done so. Where there is insufficient time to undertake baseline measures in clinic after clinic appointments, the Chief Investigator will take signed informed consent and then arrange a date to visit the patient in their own home to complete baseline measures. In this instance,

patients will be randomised to one of the two treatment arms after baseline assessment and then contacted by phone by the Chief Investigator to inform them of their randomly assigned group. The majority of the outcomes will be self-completed by the patients. The following information will be obtained:

5.4.6.1 Primary Measures:

Morisky Medication Adherence Scale:

The MMAS (Appendix 12.3) is a self-report scale for identifying medication non-adherence and has been used in PD (Morisky et al., 1986, Elm et al., 2007). The scale has 4 items which can be answered by 'yes' or 'no'. Three to four 'yes' responses would signify poor/ low adherence and four 'no' responses would signify perfect adherence. Participants scoring ≥ 1 i.e. moderate to low adherence are eligible for inclusion in the current study.

Parkinson's disease Questionnaire - 39:

The PDQ-39 (Appendix 12.11) is a PD-specific QOL questionnaire that has been developed and extensively tested for reliability and validity. It is now widely used in both research and clinical practice (Peto et al., 2001). The 39 items of the scale measure eight dimensions of health: mobility, ADL, emotional wellbeing, stigma, social support, cognition, communication and bodily discomfort.

5.4.6.2 Secondary Measures:

Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

The MDS-UPDRS (Appendix 12.12) is a recently revised and improved version of the widely used and cited disease rating scale (Goetz et al., 2007, Goetz et al., 2008). The MDS-UPDRS is comprised of 65 items and has four parts, namely, I: Non-motor Experiences of Daily Living; II: Motor Experiences of Daily Living; III: Motor Examination; IV: Motor Complications. Twenty questions are completed by the patient/caregiver. When tested for its clinimetric properties, the scale has been shown to have high internal consistency, reliability and validity, and correlates well with the original UPDRS (Goetz et al., 2008).

Part 1, 2 and 4 will be completed at each data collection point in the trial (baseline, immediately post intervention and 4 weeks post intervention). The Chief Investigator will have spent ample time in clinic with members of the clinical team using the scale to become confident with its use. Competency based training developed by the Movement Disorders Society (<http://www.movementdisorders.org/>), in addition to an online examination, have already been completed by the Chief Investigator.

Beliefs about Medication Questionnaire:

The BMQ (Appendix 12.13) is comprised of two five item scales. These assess beliefs about the necessity of prescribed medication for controlling illness and concerns about taking medications (Horne et al., 1999). Respondents rate each item on a five point Likert-type scale depending on their degree of agreement ranging from option 1 to 5 (1 being strongly disagree and 5 being strongly agree). Scores therefore range from 5 to 25 for

each of the two scales with a higher score indicating more positive attitudes towards medication. Scores obtained from each of the five items in both scales are summed.

EuroQoL EQ-5D:

The EQ-5D (Appendix 12.14) is an established, standardised generic health utility index instrument used extensively in clinical studies (Brooks, 1996). It comprises of five items covering mobility, self-care, usual activity, pain/discomfort, and anxiety/depression domains. A visual analogue scale represents one final characteristic of the instrument. It provides a simple descriptive profile and can be used to estimate a single index value for a respondent's health status and change in Quality Adjusted Life Years (QALYs). The EQ-5D is short and simple, requiring just a few minutes to complete.

Caregiving Distress Scale:

The CDS (Appendix 12.15) is a concise measure designed to assess and profile informal caregivers, with respect to stressful outcomes, and therefore provide a focus for intervention (Cousins et al., 2002). The scale was developed from various care giving measures which include a wide range of items and varying associations with distress. The CDS comprises five distinct dimensions, which make up 17 items that have a potential negative impact on caregivers. Answers are provided on a 0-4 scale.

5.4.6.3 Adverse Events Monitoring:

Adverse events will be determined at each weekly visit through a discussion between the patients/ carers and DJD. An adverse events checklist (12.16) will be completed as part of a case report form following each visit. These will be reported regularly and discussed with the supervisory and clinical team. If severe adverse events are suspected, this will be reported immediately to the trial steering committee and the participants' clinical team so appropriate action can be taken. Adverse events will be recorded from the moment patients are entered into the study (at randomisation) to the point at which they leave the study (follow-up).

All adverse events will be dealt with in strict concordance with NNUH's standard operating procedure (SOP 205) for identifying, recording, and reporting adverse events for clinical trials.

Data from studies have shown that the cognitive state and mood of someone can influence their medication adherence (Coons et al., 1994, MacLaughlin et al., 2005). Dimatteo et al (2000) reported depressed patients are three times more likely to adhere poorly to their medications than non-depressed elderly patients. Findings further show poor adherence to anti-parkinsonian medications is associated with the incidence of depression in people with PD (Grosset et al., 2005).

Additionally, cognitive impairment represents a major risk factor for non-adherence in people with PD. Such a deficit has been associated with both under and over-use of medications, suggesting it influences medication

taking behaviour (MacLaughlin et al., 2005, Bainbridge and Ruscin, 2009). It is, therefore, reasonable to presume that cognitive impairment, or the presence of anxiety and depression, may have a negative influence over how effective an adherence therapy intervention might be. Consequently, we are measuring these potential confounders at baseline.

Montreal Cognitive Assessment Scale:

The MoCa (Appendix 12.17) is a 30-point scale delivered by a rater to the patient. It covers a range of executive functions which are important to assess in PD. In a recent review - on behalf of the Parkinson's Disease Study Group - Chou et al (2010) aimed to identify the most appropriate scale for assessing cognitive impairment in PD where cognition was not the primary outcome. Findings revealed the MoCa to be the most appropriate scale in this patient population.

The scale has six orientation questions and a five word memory recall task. A clock drawing task and a cube copy test assess visuospatial function. Attention/concentration is assessed using serial 7's, and target mapping and digit span forward and backwards tasks. Confrontation naming and repetition tasks assess language. Executive functions are evaluated using a shortened version of the Trial Making B Test, phonemic fluency, and a verbal abstraction task.

Hospital Anxiety and Depression Scale:

The HADS (Appendix 12.18) is a self screening questionnaire for anxiety and depression (Zigmond and Snaith, 1983). It consists of 14 questions, seven for each anxiety and depression and has been widely used and validated (Bjelland et al., 2002). Should the HADS identify depression this information will be fed back to the patient immediately along with one of the two following actions: (1) recommending they contact their GP (moderate/severe depression) (Appendix 12.19) or (2) refers them to relevant self-help websites (mild depression) (Appendices 12.20). A letter will be posted/faxed (with the participant's knowledge) to their GP, informing them that their patient has been identified as potentially having depression (HADS score and date of completion) and informing them of what recommendations the research team has made to the patient (Appendix 12.21).

Satisfaction Questionnaire:

To investigate patient and carer satisfaction with the CAAT process, we will send out with the 4-week follow-up outcome measures a satisfaction questionnaire (Appendix 12.22).

5.4.7 Interventions

5.4.7.1 Treatment as Usual (TAU)

Patients in the TAU group will receive no additional information regarding medication adherence from the Chief Investigator or department specialist nurses. Their care will continue as usual according to routine practice. We will not provide any guidance to the clinical team as to the content of the usual care package.

5.4.7.2 Carer Assisted Adherence Therapy (CAAT)

The CAAT package has been developed by a member of the research team (RG) in conjunction with relevant clinical and lay experts. The therapy is rooted in the observation that patients' beliefs impact on their treatment adherence. Identification and amplification of the personally relevant benefits of treatment, modifying beliefs about medication and exploring ambivalence towards medication taking behaviour represent interrelated constructs that are central tenants of the therapy. The adaptability of the approach has resulted in a comprehensive, evidence-based programme capable of being tailored according to individual need and designed for delivery by a trained person. The Chief Investigator has received the appropriate training from RG.

In addition to treatment as usual, patients allocated to the CAAT arm will receive seven 20 minute sessions at weekly intervals of the intervention. Each weekly session will focus on a separate theme. Where a patient's carer has consented to the trial, AT will also be delivered to the carer at the same time with the patient. Ten sessions of CAAT over the course of the trial will be recorded to determine treatment fidelity. Participants will be made aware of this in the participant information sheet and will be asked to consent for this again at the visit.

Treatment fidelity of the CAAT intervention will be determined by audio recording a selection of sessions. These will then be assessed against the AT manual by a member of the research team who is not involved in the delivery of the therapy.

5.4.8 Follow-up

Outcome measures will be repeated immediately post intervention (after seven sessions of CAAT are completed) and at four weeks post intervention.

6 Analysis

6.1 Description of Statistical Methods

Primary and secondary outcomes will be compared between intervention and control groups using standard methods as determined by the Chief Investigator and the project statistician (AC) prior to un-blinding of the data. Where differences are observed in measures between treatment groups, demographics, and patient characteristics at baseline, an adjusted analysis will be carried out.

6.2 Baseline analyses:

To assess external generalisability, demographic and clinical characteristics of participants' responses at the baseline phase of the study will be compared to participants who are subsequently randomised and participants who are screened but not randomised. The specific criteria by which participants are excluded from randomisation will be tabulated. Demographic and clinical characteristics will be compared between the intervention and TAU groups to identify any inconsistencies that may act as potential confounders.

6.3 Power calculation

Due to the practicalities associated with visiting participants in the community over the trial data collection period, a realistic total of 92 study participants will be sought (46 for the CAAT-PARK group and 46 for the

TAU group). This includes an additional 15% (n=12) for potential subject attrition.

Using the primary outcome measures a sample size of 40 participants per group would provide an alpha of $P=0.05$ and:

a) An 81% power to detect a difference of 25% (intervention group) against 0% (control group) improvement in medication adherence as detected by the MMAS.

b) An 80% power to detect a difference of 0.69 standard deviations, or a Cohen's effect size of 0.69, as determined by the PDQ-39.

6.4 Efficacy analysis

The efficacy of the intervention on the primary outcomes (MMAS and PDQ-39) will be assessed by comparing outcomes immediately post intervention with baseline analysis and outcomes at four weeks post intervention with baseline analysis. The four week post intervention with baseline analysis will represent the primary analysis of efficacy for CAAT. These analyses will be between the two groups using an independent sample *t* test, and between participants in both groups at the three time points across the trial (i.e. baseline, immediately following intervention and four weeks post intervention) using a paired *t* test to identify change within groups. Adjusted estimates will be obtained by identifying baseline variables which differ between the groups (potential confounders) and incorporating these into a regression model using pre and post intervention primary outcome scores. If normal distribution assumptions are not met, even after suitable transformations, then a non-parametric approach will be adopted. Imputation for missing/incomplete data will be carried out using iteratively chained equations with all outcome measures and potentially correlated baseline values. A total of 10 imputed datasets will be created.

6.4.1 Inclusion in Analysis

Both intention to treat (ITT) and per protocol (PP) analyses will be performed. The ITT analysis set will comprise all patients who have been randomised to each group. For the intervention group, this is irrespective of their compliance with the planned intervention (CAAT). This is the primary analysis and will be used for evaluation of all endpoints. The PP set will include patients that have not deviated from the protocol in such a manner that the assessment of efficacy endpoints may be biased. Per protocol populations (number of CAAT sessions required to be undertaken) will be decided by a rater at the end of the data collection phase, and who is blinded to the primary outcome of individual participants. We intend to specify that if a patient or carer managed to complete five out of seven AT sessions then this will be sufficient to deem a participant as complying with the intervention. Appropriate adjustments will be made in the statistical analyses for potential confounding factors. These include age, gender, socioeconomic status, medication profile, presence of spouse or carer, occupation, level of education, cognitive capacity and level of anxiety and depression.

6.4.2 Sub-Analyses

Participants in the CAAT arm will undergo a sub-group analysis testing for an interaction between the presence of a carer on the treatment effect in a regression model. Patients in the treatment arm will be stratified into carer or no carer groups accordingly.

Baseline Anxiety and Depression

The correlation between participants' anxiety and depression (as measured by HADS) and degree of efficacy (as measured by a change from baseline of the PDQ-39 and MMAS) following the CAAT intervention will be estimated.

Baseline Cognition

The correlation between participants' level of cognitive impairment (as measured by MoCa) and degree of efficacy (as measured by change from baseline of the PDQ-39 and MMAS) following the CAAT intervention will be estimated.

6.4.3 Measuring effects

The measures of effectiveness employed in the economic analysis will be the EQ-5D (Brookes 1996). This is a generic measure of health status designed to compare the benefits of different interventions. It has five dimensions – mobility, self-care, usual activities, pain, anxiety and depression. These will be used to calculate quality-adjusted-life-years (QALYs) associated with the intervention and TAU.

6.4.4 Safety Analysis

A safety analysis will be undertaken for all adverse events which will be tabulated according to treatment received. A tabulation of all adverse events will be used for comparison. No formal statistical comparison will be made.

6.4.5 Potential Bias

The subjective nature of the self report instruments used for evaluation of the intervention is accepted and every effort will be made to minimise potential bias due to this dynamic. In particular, patients may over or under report their health status depending on the trial arm to which they have been assigned - although randomised, it will be obvious to the participants which arm of the trial they are in. Baseline primary self-report assessments will however be completed by the participants before they are randomised.

Due to the one-to-one participatory nature of the intervention, it will not be possible to blind study participants to their group allocation. Thus self-reported secondary outcomes will not be blinded.

6.5 Qualitative evaluation: acceptability of the adherence therapy

In depth semi-structured interviews will be undertaken with a purposively selected sub-sample of patients (n=10) and carers (n=10) to explore the process and experience of receiving CAAT. The aim of these interviews will be to:

Obtain insights into patients and carers experiences of using CAAT,

Consider which elements of the CAAT were perceived as being most and least helpful,
Explore the participants' perceptions of the effect that they think CAAT has had on them,
Uncover any potential barriers and road blocks to using the CAAT,
Explore how the CAAT programme could be refined and enhanced.

Methodology

In depth investigation of patients' and spouse/ carers' views and experiences will be undertaken after follow-up measures have been taken. Thirty minute semi-structured interviews will be used to address key topics and themes, including practical experiences of the CAAT regime. The aim is to illuminate the quantitative findings, and provide a broader descriptive and explanatory context for the quantitative outcome measures. Semi-structured interview questions will be provided to participants with the interview information sheet and its accompanying consent form.

Trial participants will be approached to provide written informed consent for participation in the interviews prior to follow-up. The qualitative sample will be purposively drawn. This purposive sampling will draw on priority criteria to ensure diversity in conceptually-relevant characteristics of potential participants. This will include: age, sex, severity of PD, along with other demographics.

Interview schedules will allow patients to address their own issues and concerns in a manner that is most pertinent to them, whilst also covering key relevant topics. Interviews will aim to elicit rich detailed data and will probe individuals specifically around practical issues of the CAAT protocol. Interviews will be conducted in participants' homes.

Qualitative data analysis

All interview data will be audio recorded and transcribed in full. Framework qualitative research software will be used to aid the qualitative analysis. The qualitative data will elucidate participants' experiences and views using a framework analytic approach to analysis. Initial analysis will sort the data thematically and chart key themes and experiences. Final analysis will compare key themes across the two participants – patient and carer. Such analysis will ultimately inform the study outcome of patient acceptability of AT, compared to TAU.

7 Project Timetable

The project will take place over 2.5 years (30 months) including preparation and write up/ dissemination time.

Once an eligible patient has been identified, consented, and randomised they will start the trial. As participants go through the trial, new participants will be recruited. This will continue for 12-14 months.

8 Quality Assurance Procedures

The study will be conducted in accordance with the approved protocol, International Conference of Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and relevant regulations and standard operating procedures. Regular monitoring will be performed according to ICH-GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents.

The trial will be reported in line with CONSORT 2010 guidelines (Schultz, 2010).

8.1 Roles and responsibilities

Dr Phyo Kyaw Myint (PKM), primary supervisor of the Chief Investigator (DJD), will oversee the conduct of the study. PKM will oversee recruitment of participants into the trial. PKM and Dr Katherine Deane (KD) will both act as project supervisors and oversee the running of the trial. This will be in addition to the guidance provided by the TSG. Prof Richard Gray (RG) will train DJD in the delivery of the intervention (AT). KD will provide required training to DJD for appropriate consent procedures while PKM, KD, RG and Dr Allan Clark (AC) (trial statistician) will supervise and guide DJD where necessary in the analysis.

AC will advise on data entry templates, monitor data management and check all data analysis conducted by DJD for accuracy. Two patient representatives on the TSG will advise on all aspects of the trial from the participants/patients perspective. The same individuals have assisted in the design of all information that will be viewed by trial participants. The delivery of the intervention will be undertaken by DJD.

8.2 Managing risk

The researchers will make every effort to ensure that risks are minimised and trial participants will be provided with appropriate contact details in case of emergency. Any complaints will be handled by UEA.

Patients identified as having depression will be given information sheets with recommendations for management in line with current NICE guidance (NICE 2009). In addition their GPs will be informed of their mental health status.

Due to the nature of the trial, it may become apparent that unwanted side effects are increased as a result of improved adherence to anti-parkinsonian medication. For this reason, adverse events will be monitored and recorded on an adverse events checklist at each participant contact phase throughout the course of the trial. In the unlikely event that a patient deteriorates or suffers an adverse event as a result of increased adherence to their prescription, the patient's clinical care team will be informed immediately so that appropriate action can be taken. This may warrant participants being withdrawn from further involvement in the trial. All action undertaken will adhere to NNUH's standard operating procedure (SOP 205) for identifying, recording, and reporting adverse events for clinical trials.

8.3 Trial Steering Committee

A TSC will be established to oversee the conduct and progress of the trial. The committee is expected to meet every 3-4 months for the duration of the study and will be chaired by an independent party. A brief outline of the terms of reference for the TSC and committee members is provided in (Appendix 12.23).

9 Ethics

9.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

9.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

9.3 Participant Confidentiality

All data will be handled in accordance with the Data Protection Act (1998) which requires data to be anonymised as soon as it is practical to do so. Participants will be identified only by participant ID numbers. Each participant will have a case record file containing consent forms, completed measures, adverse events sheets and demographic and other information as described. Case record files will be kept in a locked cabinet within a locked room at NNUH or UEA. Only the Chief Investigator, study supervisors and the specialist clinic nurses in MFE and neurology assisting in recruitment will have access to these. All investigators have undergone good clinical practice training and the supervisory team has extensive experience of clinical trials.

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on the CRF and any electronic database. Databases and all documents will be stored securely on a pass word protected computer or in a locked cabinet. Data may only be accessed by trial staff, authorised personnel and relevant regulatory bodies.

9.4 Identification of Depression

All data will be collected by the Chief Investigator who holds an honorary NHS research associates contract and will adhere to Trust policies. Should the HADS identify depression, this information will be fed back to the patient immediately along with one of two information sheets that recommend they contact their GP (moderate/ severe depression) or refers them to relevant self-help websites (mild depression) (Appendix 12.19 & 12.20). A letter will also be posted (with the patients' knowledge) to their GP informing them that their patient has been identified as having depression and informing them of what recommendations the research team has made (Appendix 12.21).

10 Data Handling and Record Keeping

All Investigators and staff involved with this study will comply with the requirements of the Data Protection Act (1998) with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The participants will be identified by a study specific participant number and/or code in any database. The name and any other identifying detail will NOT be included in any study data electronic file. All study data will be entered using double data entry onto secure computer systems at UEA. Computers used to collate data will have limited access measures via user names and passwords.

Study Case Report Forms (CRFs) will be completed by the Chief Investigator and stored securely at NNUH or UEA. CRF data will be audited by the project supervisors PKM and KD. At the end of the trial, participants will receive participant-friendly summaries of the study results. Study data forms and the study database will be archived. CRFs and all trial associated documents will be retained by the Principal Investigator and stored by NNUH Research and Development Unit for five years from study completion.

10.1 Access to source documents/ data

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to the hospital electronic patient records (from which medical history and previous and concurrent medication may be summarised into the CRF), audiotapes and correspondence. CRF entries will be considered source data where the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by participant number/code alone. Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Appendix 29: Favourable Ethical Opinion Letter

NRES Committee East of England - Cambridge Central

Victoria House
Capital Park
Fulbourn
Cambridge
CB21 5XB

Telephone: 01223 597685

Facsimile: 01223 597645

07 June 2011

Mr David James Daley
PhD student
Honorary Research Associate Contract at Norfolk and Norwich University Hospital
University of East Anglia
0.27 Queen's Building
Norwich, Norfolk
NR4 7TJ

Dear Mr Daley

Study title: **The use of carer assisted adherence therapy for people with Parkinson's disease (CAAT-PARK): a randomised controlled trial.**
REC reference: **11/EE/0179**

Thank you for your letter of 01 June 2011, responding to the Committee's request for further information on the above research, and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>	
Covering Letter	Mr David James Daley	18 April 2011	
Evidence of insurance or indemnity	UEA	15 April 2011	
Investigator CV	David James Daley	18 April 2011	
Letter of invitation to participant	1.0	11 April 2011	
Other: GP letter regarding their patients depression	1.0	11 April 2011	
Other: GP information letter	1.0	11 April 2011	
Other: Morisky Medication Adherence Scale	1.0	11 April 2011	
Other: adverse events checklist	1.0	11 April 2011	
Other: Trial Steering Committee Terms of Reference	1.0	11 April 2011	
Participant Consent Form: patient consent form	1.0	11 April 2011	
Participant Consent Form: spouse/carer consent form	1.0	11 April 2011	
Participant Consent Form: patient consent form for interview	1.0	11 April 2011	
Participant Consent Form: moderate to severe depression patient information sheet	1.0	11 April 2011	

Participant Consent Form: mild depression patient information sheet	1.0	11 April 2011	
Participant Consent Form: patient consent form for MMAS scale	1.0	11 April 2011	
Participant Information Sheet: spouse/carer information sheet	1.0	11 April 2011	
Participant Information Sheet: patient information sheet for interview	1.0	11 April 2011	
Participant Information Sheet: spouse/carer information sheet for interview	1.0	11 April 2011	
Participant Information Sheet: spouse/carer consent form for interview	1.0	11 April 2011	
Participant Information Sheet: patient information sheet	2.0	01 June 2011	
Protocol	1.0	11 April 2011	
Questionnaire: Parkinson's disease questionnaire - 39	1.0	11 April 2011	
Questionnaire: Movement Disorder Society - unified Parkinson's disease rating scale (MDS-UPRS) parts 1,2,4	1.0	11 April 2011	
Questionnaire: beliefs about medication questionnaire	1.0	11 April 2011	
Questionnaire: EQ-5D	1.0	11 April 2011	
Questionnaire: Carer distress scale	1.0	11 April 2011	
Questionnaire: Hospital anxiety and depression scale	1.0	11 April 2011	
Questionnaire: Montreal cognitive assessment	1.0	11 April 2011	
Questionnaire: satisfaction questionnaire - person with Parkinson's disease	1.0	11 April 2011	
Questionnaire: satisfaction questionnaire - carers	1.0	11 April 2011	
REC application	67978/208129/1/118	20 April 2011	
Response to Request for Further Information	David James Daley	01 June 2011	

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "*After ethical review – guidance for researchers*" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

11/EE/0179

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

**Dr Carolyn Read
Chair**

Email: Nicky.Storey@eoe.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: Miss Tracy Moulton
Research, Enterprise & Engagement Office
The Registry
University of East Anglia
Norwich
NR4 7TJ

Kath Andrews
Research and Development Office
Level 3 East
Norfolk & Norwich University Hospital
Colney Lane
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NORFOLK
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Appendix 30: Favourable Ethical Opinion for Inclusion Criteria Amendment



National Research Ethics Service
NRES Committee East of England - Cambridge Central

Victoria House
Capital Park
Fulbourn
Cambridge
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Tel: 01223 597685
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29 November 2011

Mr David James Daley
Ph.D student

Honorary Research Associate Contract at Norfolk and Norwich University Hospital
University of East Anglia
0.27 Queen's Building
Norwich, Norfolk
NR4 7TJ

Dear Mr Daley

Study title: The use of carer assisted adherence therapy for people with Parkinson's disease (CAAT-PARK): a randomised controlled trial.
REC reference: 11/EE/0179
Amendment number: Amendment 2
Amendment date: 09 November 2011
Amendment details: Lower the MMAS for study eligibility from ≥ 2 'yes' responses to ≥ 1 'yes' responses.

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Letter from Tracy Moulton authorising the amendment		09 November 2011
Details of changes to the Protocol	1.0	07 November 2011
Notice of Substantial Amendment (non-CTIMPs)	Amendment 2	09 November 2011
Covering Letter	David Daley	09 November 2011

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

This Research Ethics Committee is an advisory committee to the East of England Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within
the National Patient Safety Agency and Research Ethics Committees in England

Appendix 31: Favourable Ethical Opinion Letter for Re-starting Recruitment



Health Research Authority

NRES Committee East of England - Cambridge Central

Victoria House
Capital Park
Fulbourn
Cambridge
CB21 5XB

Tel: 01223 597685
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30 April 2012

Mr David James Daley
Ph.D student
Honorary Research Associate Contract at Norfolk and Norwich University Hospital
University of East Anglia
0.27 Queen's Building
Norwich, Norfolk
NR4 7TJ

Dear Mr Daley

Study title: The use of carer assisted adherence therapy for people with Parkinson's disease (CAAT-PARK): a randomised controlled trial.
REC reference: 11/EE/0179
Amendment number: Amendment 3 (REC #6)
Amendment date: 24 April 2012
Amendment summary: Amendment to restart the study following temporary halt following breach of protocol.

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Notice of Substantial Amendment (non-CTIMPs)	Amendment 3 (REC #6)	24 April 2012

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

11/EE/0179:	Please quote this number on all correspondence
--------------------	---

Yours sincerely



Mrs Carolyn Read
Chair

E-mail: Nicky.Storey@eoe.nhs.uk

Enclosures: List of names and professions of members who took part in the review

Copy to: Sue Steel
Research, Enterprise & Engagement Office
The Registry
University of East Anglia
Norwich
NR4 7TJ

Kath Andrews
Research and Development Office
Level 3 East
Norfolk & Norwich University Hospital
Colney Lane
Norwich
NORFOLK, NR4 7UY

Appendix 32: NNUH R&D Letter for Re- starting Trial Recruitment



Our Vision
To provide every patient
with the care we want
for those we love the most

Norfolk and Norwich University Hospitals 
NHS Foundation Trust

Mr David Daley
University of East Anglia
0.27 Queens Building
Norwich
NR4 7TJ

Research & Development Office
Level 3 East
Norfolk & Norwich University Hospitals NHS Foundation Trust
Colney Lane
Norwich
NR4 7UY

direct dial: 01603 287806
direct fax: 01603 289800
e-mail: rdoffice@nnuh.nhs.uk
website: www.nnuh.nhs.uk

27 April 2012

Dear Mr Daley,

Re: R&D Reference Number: 2011MFE03S (79-06-11)
Project Title: The use of carer assisted adherence therapy for people with Parkinson's disease (CAATPARK): a randomised controlled trial.

Thank you for recent correspondence regarding amendment 3 for the above study.

Following the completion of all required training we have no objection to this amendment, subject to the relevant regulatory approvals. If we have not already received copies of the regulatory approvals these must be sent to us at the above address when in place.

If you have any queries regarding this or any other project please contact Clare Collum, Research Facilitator, at the above address. Please note, the reference number for this study is **2011MFE03S (79-06-11)** and this should be quoted on all correspondence.

Yours sincerely



Kath Andrews
Research & Development Manager

Carbon Copy: (Sponsors Representative) Sue Steel, (Student Supervisor) Dr Phyo Myint

Appendix 33: Patient Information Sheet for Interviews



Movement Disorder Clinic,
Medicine for the Elderly
East Block, Level 3,
Norfolk and Norwich University Hospital
Colney Lane
Norwich. NR4 7UY
Tel: 01603 288173

Patient Information Sheet for Interview

The use of carer assisted adherence therapy for people with Parkinson's disease and their carers.

We would like to invite you to take part in a short interview. The interview will be around 30 minutes in duration.

We would also like to invite the person who received the 'carer assisted adherence therapy' treatment with you i.e. your spouse/ carer.

The interview will be conducted by David (Chief Investigator) who has been visiting you for seven weeks to deliver the 'carer assisted adherence therapy'. As before, there is no obligation to take part and your care will not be affected. Enclosed with this information is a brief outline of the sort of questions we will ask you in the interview.

The interview will resemble a very informal discussion about your experiences of receiving the carer assisted adherence therapy treatment. You and your spouse/ carer will be able to comment both on what you liked and didn't like about the experience. Information gathered will be used in the future to try and improve the therapy.

The interview will need to be audio recorded, however, we will ensure that any personal information will not be identifiable. Direct quotes may be used in published findings or in a submitted thesis to the University of East Anglia. Again, these will not be identifiable.

All data will be stored according to the Data Protection Act (1998).

Please do not hesitate to contact us if you require further information.

Should you have any questions please feel free to contact David (Chief Investigator) on Tel: 01603 593665, Monday – Friday, office hours. Alternatively, you could contact David's supervisor, Dr Phyo Myint on Tel: 01603 286286. We will be happy to answer any questions or concerns you might have before consenting to participate or throughout the duration of the study.

Semi - Structured Interview Questions for Determining the Participants' Acceptability of Carer Assisted Adherence Therapy

What did you think about carer assisted adherence therapy?

How do you feel David's communication style affected your satisfaction with the whole process?

What was it like to receive the therapy in your own home?

What were your expectations from the carer assisted adherence therapy before the start of the study?

Do you think the carer assisted adherence therapy met your expectations? Can you explain how?

Do you think carer assisted adherence therapy made you more or less likely to take your medication? Can you explain?

Do you feel you got some benefit from talking with David about your medication? How/ can you explain?

Do you think involving your spouse/ carer improved the whole therapy process? How/ can you explain?

Which aspect of the adherence therapy do you feel you got more benefit from? How/ can you explain?

How do you feel the carer assisted adherence therapy could be improved?

What are your thoughts about the length of the carer assisted adherence therapy (i.e. seven weeks and 20 minutes per session)? Would you of preferred more or less time?

In the future, if adherence therapy was offered as part of usual care for people who have Parkinson's disease, would you be interested in receiving the therapy? How do you think this would help you?

Appendix 34: Spouse/carer Information Sheet for Interviews



Movement Disorder Clinic,
Medicine for the Elderly
East Block, Level 3,
Norfolk and Norwich University Hospital
Colney Lane
Norwich. NR4 7UY
Tel: 01603 288173

Spouse/Carer Information Sheet for Interview

The use of carer assisted adherence therapy for people with Parkinson's disease and their carers.

We would like to invite you to take part in a short interview. The interview will be around 30 minutes in duration. We would also like to invite the person who received the 'carer assisted adherence therapy' treatment with you i.e. your spouse/relative who has Parkinson's disease.

The interview will be conducted by David (Chief Investigator) who has been visiting you for seven weeks to deliver the carer assisted adherence therapy. As before, there is no obligation to take part and your spouse's/ relative's care will not be affected. Enclosed with this information is a brief outline of the sort of questions we will ask you in the interview.

The interview will resemble a very informal discussion about your experiences of receiving the carer assisted adherence therapy. You and your spouse/ relative will be able to comment both on what you liked and didn't like about the experience. Information gathered will be used in the future to try and improve the therapy.

The interview will need to be audio recorded, however, we will ensure that any personal information will not be identifiable. Direct quotes may be used in published findings or in a submitted thesis to the University of East Anglia. Again, these will not be identifiable.

All data will be stored according to the Data Protection Act (1998). Please do not hesitate to contact us if you require further information. You can also refer to the information sheet we provided you with before you started the study.

Should you have any questions please feel free to contact David (Chief Investigator) on Tel: 01603 593665, Monday – Friday, office hours. Alternatively you could contact David's supervisor Dr Phyto Myint on Tel: 01603 286286. We will be happy to answer any questions or concerns you might have before consenting to participate or throughout the duration of the study.

Appendix 35: Patient Interview Consent Form



Movement Disorder Clinic,
Medicine for the Elderly
East Block, Level 3,
Norfolk and Norwich University Hospital
Colney Lane
Norwich. NR4 7UY
Tel: 01603 288173

Date.....

Assigned Clinic Number:

***The use of carer assisted adherence therapy for people with Parkinson’s disease and their carers:
Interview***

(Please initial box)

I confirm that I have read and understood the information sheet Dated 01/06/11 (version 2.0) for taking part in an interview for the above study.

I have had the opportunity to consider the information and ask questions.

I understand that my participation in the interview is voluntary and that I can withdraw at any time without my medical care or legal rights being affected.

I agree to have the interview audio recorded.

I agree that the research team may publish direct quotes from my interview. I understand that these quotes will not identify me in any way.

I agree to my GP being informed of my participation.

I understand that my collected data may be looked at by authorised individuals at the University of East Anglia, however, this would be anonymous.

I understand that all storage of my personal information must comply with the Data Protection Act (1998).

I agree to take part in the interview.

Participant's Name

.....

Participant's Signature

.....

Date

.....

Chief Investigator's Name

.....

Chief Investigator's Signature

.....

Date

.....

Appendix 36: Spouse/carer Interview Consent Form



Movement Disorder Clinic,
Medicine for the Elderly
East Block, Level 3,
Norfolk and Norwich University Hospital
Colney Lane
Norwich. NR4 7UY
Tel: 01603 288173

Date.....

Spouse/ Carer Consent Form for Interview

Assigned Clinic Number:

***The use of carer assisted adherence therapy for people with
Parkinson’s disease and their carers:
Interview***

(Please initial box)

- I confirm that I have read and understood the information sheet Dated 01/06/11 (version 2.0) for taking part in an interview for the above study.
- I have had the opportunity to consider the information and ask questions.
- I understand that my participation in the interview is voluntary and that I can withdraw at any time without my spouse’s/relative’s medical care or legal rights being affected.
- I agree to have the interview audio recorded.
- I agree that the research team may publish direct quotes from my interview. I understand that these quotes will not identify me in any way.

• I understand that my collected data may be looked at by authorised individuals at the University of East Anglia, however, this would be anonymous.

• I understand that all storage of my personal information must comply with the Data Protection Act (1998).

• I agree to take part in the interview.

Participant's Name

.....

Participant's Signature

.....

Date

.....

Chief Investigator's Name

.....

Chief Investigator's Signature

.....

Date

.....

Appendix 37: Interview Questions

Interview Questions

What did you find most helpful and least helpful?

When you started the programme, what were your expectations?

What happened that you did and didn't like?

What did you think about session duration/ environment and input of carer?

What have you learnt? Has it changed the way you view your medication?

How could the therapy be improved if at all?

Would you recommend the therapy?

Between the sessions did you think about what was talked about? How did it make you feel?

How have the sessions, if at all, made you think about your Parkinson's disease?

Has the way you perceive your medication changed? How?

Appendix 38: Example of Codes and Code Descriptions

Code	Description	Occurrences in Data
Knowledge	AT useful for explaining nature of PD	22
Poor prior K + U	No information given about drug use and its effects in PD which AT helped with	13
Poor prior K + U	Pt unaware of need for timing meds	16
↑ understanding	Pt acknowledges past experiences being PD related	5
↑ understanding ↑ confidence	Reinforced what was already known	2
↑ ability to cope	Pt felt AT has been useful for coping in daily in general	3
↑ K + U	Pt realises alternative explanations for poor symptom control are not correct. Acceptance of med efficacy	4
AT – flexible range of topics	Different topics were covered as part of AT	4
Open/honest	Openness and honesty to facilitate AT helped	7
↑ acceptance	Being able to finally talk about PD, not keeping it locked away	5
Flexibility	Liked flexibility of sessions	5
Trust	Pt could be open up due to greater element of trust than other professionals	6
Specialist knowledge	Someone who understands and can empathise	5
Interest	Gave time and consideration so pt believed therapist was interested	8
Specialist knowledge	Confident in therapists knowledge which encouraged pt	6
Openness Interested	Asking questions in a way that made pt want to give answers.	4
Openness Interested	Question style made pt question their own perspective	5

Appendix 39: Extract of an Interview Transcript

Respondent 2 and Spouse

DD: What did you find most and least helpful about the whole process?

BG: I found it very helpful in helping me understand why you take medicine on time. There wasn't anything I found unhelpful.

WG: Same here, I think it helped Brian a great deal.

DD: Were there any specific weeks that stood out more than others?

BG: Err, peaks and trough obviously and getting into a habit that gave me some sort of signal that told me it was time to take my medication.

DD: That was the alarm as it? Did you find that quite helpful then?

BG: I still use it. It works wonders. Even now sometimes I'm walking through the doors just before the alarm is going off. I know it's time.

DD: So you're remembering?

WG: Except for a couple of times.

BG: I have the odd blip.

WG: When the grandson had been talking to him and he's switched the alarm off and then walked out and forgot the tablets. So many hours later he's suffered. Then it clicked and he swore at himself.

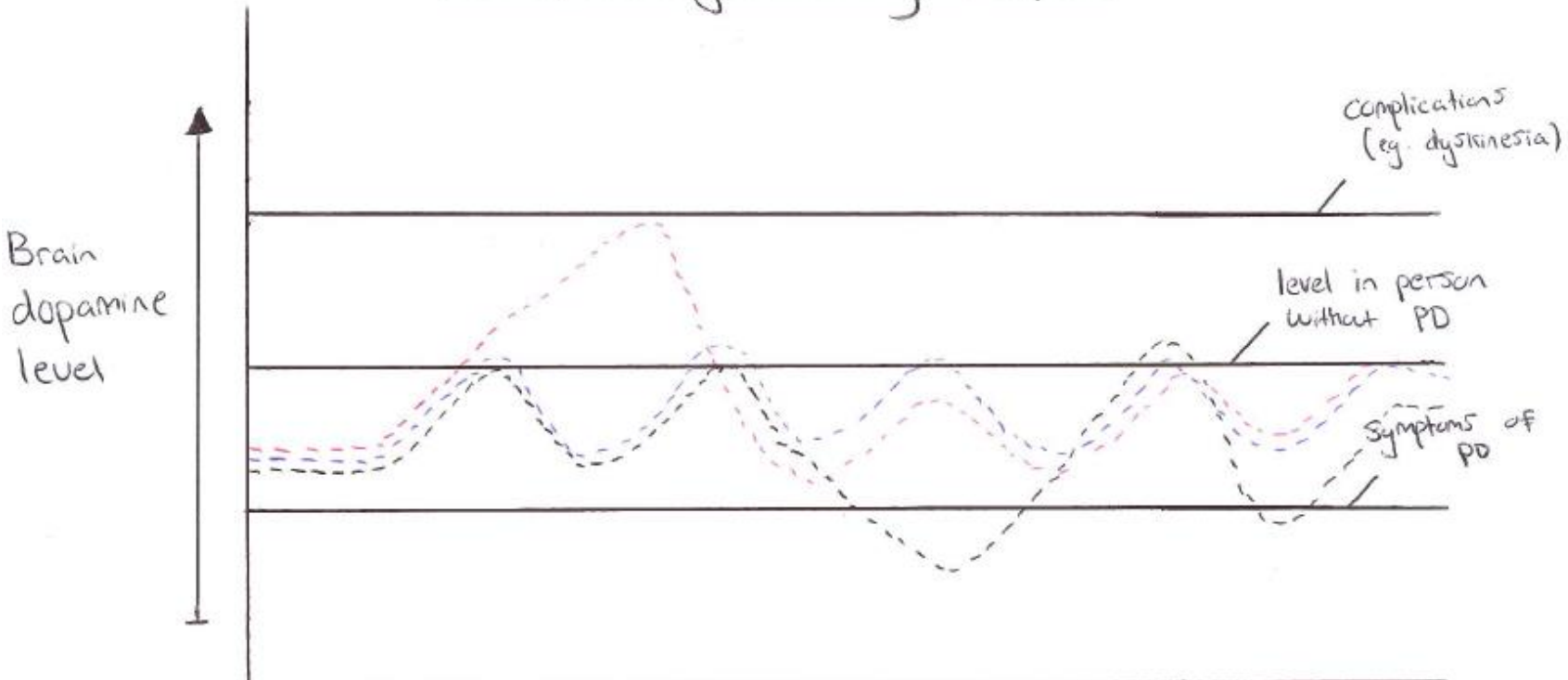
BG: The things I've learnt out of that is don't switch the alarm off until you've taken the pills. If you've switched it off your brain goes 'done, time to go'.

DD: When we started when I first came to see you what were your expectations?

BG: I hadn't got a clue. I was asked if I'd volunteer. I met you at the hospital with the questions. I hadn't got any idea in-depth.

Appendix 40: Diagram of Dopaminergic Theory Used for Explanation

Dopaminergic Theory Graph



Daily Dose Timing

- : correct dose timing
- : dosing times too close
- . - . : late dose timing

Appendix 41: Published Papers