N-DOSE: A randomized, double blind, dose optimization trial of nicotinamide riboside in Parkinson's disease.

Protocol Identification Number: v3.1, 5th June 2025

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PROTOCOL VERSION NO. 3.1, -June 2025

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SIGNATURE PAGE

Title **N-DOSE: A randomized, double blind, dose optimization trial of nicotinamide riboside in Parkinson's disease.**

Protocol ID no:

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

To be signed by sponsor's representative, Coordinating Investigator, Principal Investigator, statistician etc. This section and table above should be completed as appropriate for the type of study conducted and the parties involved.

Name	Title	Role	Signature	Date
Torhild Næss Vedeler	Neurology clinic Director	Sponsor representative		
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PROTOCOL SYNOPSIS

N-DOSE: A randomized, double blind, dose optimization trial of nicotinamide riboside in Parkinson's disease.

Sponsor:	Haukeland University Hospital
Phase and study type:	Phase II, Dose-Optimization study
Investigational Product (IP) (including active comparator and placebo):	Nicotinamide Riboside, Placebo
Centers:	**Haukeland University Hospital**
Study Period:	Estimated date of first patient enrolled: 28.11.2022 Anticipated recruitment period: 01.10.2022 – 20.01.2025. Estimated date of last patient completed: 22.04.2025.
Treatment Duration:	12 weeks

Objectives and endpoints

Objective		**Endpoint**
Primary	To compare the effect of orally administered nicotinamide riboside (NR), escalated to 1500 mg twice per day (3000 mg/day) in the dose-escalation group (DE-group) - versus stable dosing of 500 mg twice per day (1000 mg/day) in the dose-stable group (DS-group) on cerebral NAD-levels, at week 12.	Change in cerebral NAD/ATP-α ratio measured by 31 Phosphorus magnetic resonance spectroscopy (31P-MRS) in the posterior brain (encompassing the occipital, parietooccipital and posterior parts of the temporal cortex).
Secondary	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in cerebral NAD levels from baseline to weeks 4, 8 and 12.	Change in cerebral NAD/ATP-α ratio measured by 31 Phosphorus magnetic resonance spectroscopy (31P-MRS) in the posterior brain (encompassing the occipital, parietooccipital and posterior parts of the temporal cortex).
	To compare the effectiveness of orally administered nicotinamide riboside (NR) 1500 mg twice per day versus 500 mg twice per day in augmenting the NAD-metabolome in the central nervous system (CNS) at week 12.	Change in the cerebrospinal fluid (CSF) levels of NAD or other metabolites of the NAD metabolome*, measured by LC-MS.

Exploratory	**Neuroimaging**	
	To compare the effect of orally administered NR in the DE-group versus DS-group on the NR related metabolic pattern (NRRP) expression at week 12.	Change in NRRP expression, measured by FDG-PET.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in NRRP expression from baseline to weeks 4, 8 and 12.	Change in NRRP expression, measured by FDG-PET.
	To compare the effect of orally administered NR DE-group versus DS-group on the PD-related pattern (PDRP) expression at week 12.	Change in PDRP expression, measured by FDG-PET.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in PDRP expression from baseline to weeks 4, 8 and 12.	Change in PDRP expression, measured by FDG-PET.
	Metabolism & molecular markers	
	To compare the effect of orally administered NR in the DE-group versus DS-group on the NAD metabolome* in the blood, urine and central nervous system (CNS) at week 12.	Change in levels of NAD metabolites in blood, urine and CSF, measured by HPLC-MS and/or the NADMed method.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in the NAD metabolome* in blood and urine from baseline to weeks 4, 8 and 12.	Change in levels of NAD metabolites in blood and urine, measured by HPLC-MS and/or the NADMed method.
	To compare the effect of orally administered NR in the DE-group versus DS-group on serum and CSF inflammatory markers at week 12.	Change in inflammatory cytokines in serum and CSF, measured by ELISA.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in serum inflammatory markers from baseline to weeks 4, 8 and 12.	Change in inflammatory cytokines in serum, measured by ELISA.
	Clinical – motor & non motor symptom severity, quality of life	
	To compare the effect of orally administered NR in the DE-group versus DS-group on clinical severity of PD symptoms at week 12.	Change in the total MDS-UPDRS score in the ON-medication state.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and change in clinical severity of PD symptoms from baseline to weeks 4, 8 and 12.	Change in total MDS-UPDRS score in the ON-medication state.
	To compare the effect of orally administered NR in the DE-group versus DS-group on severity of non-motor symptoms of daily living in PD at week 12.	Change in the MDS-UPDRS part I score in the ON-medication state.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and change in severity of non-motor symptoms of daily living in PD from baseline to weeks 4, 8 and 12.	Change in the MDS-UPDRS part I score in the ON-medication state.
	To compare the effect of orally administered NR	Change in the MDS-UPDRS part II score in the ON-

	in the DE-group versus DS-group on severity of motor aspects of experiences of daily living in PD at week 12.	medication state.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in severity of motor aspects of experiences of daily living in PD from baseline to weeks 4, 8 and 12.	Change in the MDS-UPDRS part II score in the ON-medication state.
	To compare the effect of orally administered NR in the DE-group versus DS-group on severity of PD motor symptoms at week 12.	Change in the MDS-UPDRS part III score in the ON-medication state.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in severity of PD motor symptoms from baseline to weeks 4, 8 and 12.	Change in the MDS-UPDRS part III score in the ON-medication state.
	To compare the effect of orally administered NR in the DE-group versus DS-group on severity PD motor complications at week 12.	Change in the MDS-UPDRS part IV score in the ON-medication state.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in severity of PD motor complications from baseline to weeks 4, 8 and 12.	Change in the MDS-UPDRS part IV score in the ON-medication state.
	To compare the effect of orally administered NR in the DE-group versus DS-group on clinical severity of PD non-motor symptoms at week 12.	Change in the total MDS-NMS score.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in clinical severity of PD non-motor symptoms from baseline to weeks 4, 8 and 12.	Change in the total MDS-NMS score.
	To compare the effect of orally administered NR in the DE-group versus DS-group on clinical severity of gastrointestinal non-motor dysfunction in PD at week 12.	Change in the modified GIDS-PD score.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in clinical severity of gastrointestinal non-motor dysfunction in PD from baseline to weeks 4, 8 and 12.	Change in the modified GIDS-PD score.
	To compare the effect of orally administered NR in the DE-group versus DS-group on cognition at week 12.	Change in the MoCA score.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in cognition from baseline to weeks 4, 8 and 12.	Change in the MoCA score.
	To compare the effect of orally administered NR in the DE-group versus DS-group on quality of life in PD at week 12.	Change in the EQ-5D-5L score.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg	Change in the EQ-5D-5L score.

	per day) and changes in quality of life in PD from baseline to weeks 4, 8 and 12.	
	Hypothesis-generating or resource-dependent endpoints (may be reported in follow-up or secondary publications).	
	To compare the effect of orally administered NR in the DE-group versus DS-group on gene expression at week 12.	Change in gene expression, measured by RNA sequencing (RNAseq).
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in gene expression from baseline to weeks 4, 8 and 12.	Change in gene expression, measured by RNA sequencing (RNAseq).
	To compare the effect of orally administered NR in the DE-group versus DS-group on protein expression at week 12.	Change in protein levels, measured by LC-MS.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in protein expression from baseline to weeks 4, 8 and 12.	Change in protein levels, measured by LC-MS.
	To compare the effect of orally administered NR in the DE-group versus DS-group on serum and CSF inflammatory markers at week 12.	Change in inflammatory cytokines in serum and CSF, measured by ELISA.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in serum inflammatory markers from baseline to weeks 4, 8 and 12.	Change in inflammatory cytokines in serum, measured by ELISA.
	To compare the effect of orally administered NR in the DE-group versus DS-group on histone acetylation in PD at week 12.	Change in histone panacetylation, measured by immunoblotting.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in histone acetylation in PD from baseline to weeks 4, 8 and 12.	Change in histone panacetylation, measured by immunoblotting.
	To compare the effect of orally administered NR in the DE-group versus DS-group on H3K27 and H4K16 histone acetylation in PD at week 12.	Changes in levels of H3K27 and H4K16 acetylation, measured by immunoblotting.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in on H3K27 and H4K16 histone acetylation in PD from baseline to weeks 4, 8 and 12.	Changes in levels of H3K27 and H4K16 acetylation, measured by immunoblotting.
	To compare the effect of orally administered NR in the DE-group versus DS-group on the genomic distribution of H3K27 and H4K16 histone acetylation in PD at week 12.	Change in the genomic distribution of H3K27 and H4K16 acetylation, measured by chromatin immunoprecipitation sequencing (ChIPseq).
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in the genomic distribution of H3K27 and H4K16 histone acetylation in PD from baseline to weeks 4, 8 and 12.	Change in the genomic distribution of H3K27 and H4K16 acetylation, measured by chromatin immunoprecipitation sequencing (ChIPseq).
	To compare the effect of orally administered NR in the DE-group versus DS-group on folate and	Change in folate and one-carbon metabolites in blood and CSF, measured by HPLC-MS.

	one-carbon metabolism in PD at week 12.	
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in folate and one-carbon metabolism in PD from baseline to weeks 4, 8 and 12.	Change in folate and one-carbon metabolites in blood, measured by HPLC-MS.
	To compare the effect of orally administered NR in the DE-group versus DS-group on methyl donors in PD at week 12.	Change in methyl-donors (e.g., SAM), measured by HPLC-MS, in the blood and/or CSF.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in methyl-donors in PD from baseline to weeks 4, 8 and 12.	Change in methyl-donors (e.g., SAM), measured by HPLC-MS, in the blood.
	To compare the effect of orally administered NR in the DE-group versus DS-group on DNA methylation at week 12.	Change in level and genomic distribution of DNA methylation, measured by Illumina Infinium MethylationEpic kit.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in methyl-donors in PD from baseline to weeks 4, 8 and 12.	Change in level and genomic distribution of DNA methylation, measured by Illumina Infinium MethylationEpic kit.
	To compare the effect of orally administered NR in the DE-group versus DS-group on synthesis of neurotransmitters in PD at week 12.	Change in neurotransmitters in CSF, measured by HPLC-MS.
	Determine whether NR-therapy affects the gut microbiome in a dose-responsive manner at week 12.	Change in gut microbiome composition, measured by metagenomics in fecal samples.
	To compare the effect of orally administered NR in the DE-group versus DS-group on the gut metabolome at week 12.	Change in fecal metabolomics, measured by LC-MS in fecal samples.
	To compare the effect of orally administered NR in the DE-group versus DS-group on the sense of smell at week 12.	Change in sense of smell, measured by B-SIT score.
Safety	To determine the safety and tolerability of NR at a dose of 1000 mg, 2000 mg, and 3000 mg per day in PD.	Number and severity of adverse events from baseline to week 12 across treatment groups and NR dose levels.

***The NAD metabolome is comprised of:** Nicotinamide adenine dinucleotide oxidized (NAD^+), Nicotinamide adenine dinucleotide reduced (NADH), NAD^+/NADH ratio, total NAD (sum of NAD^+ and NADH), Nicotinamide adenine dinucleotide phosphate oxidized ($NADP^+$), Nicotinamide adenine dinucleotide phosphate reduced (NADPH), $NADP^+$/NADPH ratio, total NADP (sum of $NADP^+$ and NADPH, 1-methyl nicotinamide (Me-Nam), nicotinic acid-adenine dinucleotide (NAAD), N1-methyl-2-pyridone-5-carboxamide (Me-2-PY), Nicotinamide (Nam), Nicotinamide N-oxide (Nam N-oxide), ADP-ribose (ADPR), Nicotinic acid riboside (NAR), Nicotinamide riboside (NR), Nicotinamide mononucleotide (NMN), Nicotinic acid (NA).

Study Design: Single-center, double-blinded, randomized, placebo controlled, dose-optimization

Inclusion Criteria:	• Clinically established diagnosis of idiopathic PD according to the MDS criteria. • 123I-Ioflupane dopamine transporter imaging (DAT-scan) or 18-F-FDOPA positron emission tomography imaging (18F-FDOPA PET) confirming nigrostriatal degeneration. • Hoehn and Yahr score < 4 at enrollment. • Age ≥ 40 years at the time of enrollment. • Able to undergo lumbar punction. • Able to undergo MRI
Exclusion Criteria:	• Dementia or other neurodegenerative disorder at baseline visit. • Diagnosed with atypical parkinsonism (PSP, MSA, CBD) or vascular parkinsonism. • Any psychiatric disorder that would interfere with compliance in the study. • Metabolic, neoplastic, or other physically or mentally debilitating disorder at baseline visit. • Use of high dose vitamin B3 supplementation within 30 days of enrollment
Sample Size:	80 patients (20 in placebo group, 60 in treatment groups)
Efficacy Assessments:	Primary endpoint: Cerebral NAD levels as measured by ^{31}P-MRS (see details under Endpoints).
Safety Assessments:	Biochemistry: Routine blood analysis (see Lab-manual). Vital signs: pulse, blood pressure. Registration of adverse events.

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List of Abbreviations and Definitions of Terms

Abbreviation or special term	Explanation
AE	Adverse Event
ChIPseq	Chromatin immunoprecipitation sequencing
CNS	Central Nervous System
CRF	Case Report Form (electronic/paper)
CSF	Cerebrospinal fluid
SAM	S-denosyl methionine
DS-group	Dose-stable group
DE-group	Dose-escalation group
CSA	Clinical Study Agreement
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation due to Adverse Event
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
EQ-5D-5L	A standardized measure of health-related quality of life
GCP	Good Clinical Practice
GIDS-PD	Gastrointestinal Dysfunction Scale for Parkinson's Disease
HPLC-MS	High pressure liquid chromatography-mass spectrometry
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IP	Investigational Product (includes active comparator and placebo)
IND	Investigational New Drug
LC-MS	Liquid chromatography-mass spectrometry
HPLC-MS	High performance liquid chromatography-mass spectrometry
MDS-CDC	Movement Disorders Society – Clinical Diagnosis Criteria for PD
MDS-NMS	Movement Disorders Society – Non-Motor rating Scale
MDS-UPDRS	Movement Disorders Society – Unified Parkinson's Disease Rating Scale
MDS-NMS	Movement Disorders Society – Non-Motor rating Scale

MoCA	Montreal Cognitive Assessment
MRS-responder	An individual susceptible to NR-induced increase in cerebral NAD levels, detectable by ^{31}P-MRS
MRS-non-responder	An individual showing no NR-induced increase in cerebral NAD levels, detectable by ^{31}P-MRS
NAD	Nicotinamide adenine dinucleotide
NR	Nicotinamide Riboside
NRRP	NR-related metabolic pattern
PDRD	Parkinson's disease related pattern
OBD	Optimal biological dose
PBMC	Peripheral Blood Mononuclear Cells
PD	Parkinson's Disease
PDRP	Parkinson's Disease-Related Pattern
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

1 INTRODUCTION

1.1 Background – Disease

1.1.1 Parkinson's disease (PD) is a major societal challenge

PD affects 1-2% of the population above the age of 65, and is a major cause of death and disability with a devastating global socioeconomic impact[1,2]. In Europe alone, PD affects an estimated 1.2 million people and has a cost of €14 billion per year[3]. Current treatments for PD are purely symptomatic and have no impact on disease progression. As a result, patients confront a future of progressive disability, early institutionalization, and premature death. Since demographic studies show that patient numbers will continue to grow, effectively doubling by 2040, our failure to make any significant impact to halt or delay disease progression means that PD is now a **major challenge** to health care and society.

1.2 Background - Therapeutic Information

1.2.1 NAD-replenishment therapy shows promise as neuroprotective therapy for PD

Increasing evidence supports that boosting cellular levels of nicotinamide adenine dinucleotide (NAD) confers neuroprotective effects in both healthy aging and neurodegeneration[4]. NAD, which constantly shuttles between its oxidized (NAD^+) and reduced (NADH) state, is an essential cofactor for metabolic redox reactions, including mitochondrial respiration. Furthermore, NAD^+ is substrate to vital signaling reactions involved in DNA repair, histone- and other protein deacylation, and second messenger generation[5]. These reactions consume NAD^+ at high rates, requiring constant replenishment via NAD biosynthesis. NAD levels have been shown to decline with age and this is believed to contribute to age-related diseases[5,6]. Increasing the NAD replenishment rate (e.g., via supplementation of precursors), and/or enhancing the NAD^+/NADH ratio (e.g., via caloric restriction) have shown beneficial effects on life- and healthspan in multiple model systems, and evidence of neuroprotection in models of neurodegeneration and other age-related diseases[5–7]. Enhancing NAD replenishment could potentially help ameliorate several major processes implicated in the pathogenesis of PD, including mitochondrial respiratory dysfunction[8–10], neuroinflammation[11], epigenomic dysregulation[12,13] and increased neuronal DNA damage[14].

NAD can be replenished via supplementation of nicotinamide riboside (NR), a vitamin B3 molecule and biosynthetic precursor of NAD[5,15]. NR has undergone extensive preclinical testing[16] and is well tolerated by adult humans, showing no evidence of toxicity with doses up to at least 2000 mg daily[17].

1.2.2 Investigational Product (IP)

NR (Niagen®, Chromadex) is fully approved for human use and no evidence of toxicity has been found. NR has undergone extensive preclinical testing[16] and is Generally Recognized as Safe (GRAS) for use in food products by the United States Food and Drug Administration[31] and by the European Food Safety Authority[32]. NR is well tolerated with no evidence of toxicity in adult humans with doses up to at least 3,000 mg daily[16–21]. This evidence includes our recently concluded safety and tolerability trial NR-SAFE (clinicaltrials.gov: NCT05344404), which revealed no adverse events of clinical relevance with 3000mg NR daily for 30 days (manuscript in preparation). We therefore propose that dosages up to 3000 mg is highly unlikely to cause evidence of toxicity. Niagen and placebo will be provided from Chromadex, https://chromadex.com/. Active study drug capsules will contain 250 mg NR. Placebo will contain

microcrystalline cellulose, which will be identical in appearance and taste.

1.3 Pre-Clinical & Clinical Experience with Investigational Product (IP)

1.3.1 Preclinical evidence for NR-therapy

Trials in healthy individuals have shown that oral intake of 1000 mg NR daily substantially elevates total levels of NAD and related metabolites in blood and muscle, boosts mitochondrial bioenergetics and decreases circulating inflammatory cytokines[19,22–24]. Moreover, evidence from cell and animal studies suggests that NR supplementation promotes healthspan and has neuroprotective effects in models of Cockayne syndrome[25], noise-induced injury[26,27], amyotrophic lateral sclerosis[28], Alzheimer's disease [29,30] and PD[31].

1.3.2 Phase I evidence for NR-therapy in PD

Two phase I studies of NR in PD have been completed, the **NADPARK**[18,32] study and the **NR-SAFE**[21] study. These are described briefly below.

I. The NADPARK study (ClinicalTrials.gov: *NCT03816020*)[32] is a phase I randomized, double blinded trial, aiming to assess the tolerability, cerebral bioavailability and molecular effects of NR therapy in PD. A total of 30 individuals with newly diagnosed, drug-naïve PD were randomized to NR 500 mg x2/day or placebo for 30 days. The study showed promising results, which were published in 2022[18] and are briefly summarized below:

1) NR is well-tolerated: NR 1000 mg per day has excellent compliance, tolerability and no signs of toxicity or adverse effects in PD.

2) NR achieves brain penetration: *In vivo* measurement of cerebral NAD levels using phosphorus magnetic resonance spectroscopy (31P-MRS) of the brain showed a highly significant (paired t-test: P = 0.016) **increase in cerebral NAD levels** in the NR group, while no change was observed in the placebo group **(Fig 1A-C)**. Cerebral penetration was further validated by detecting the metabolite Me-2-PY in the CSF of participants receiving NR, but not placebo **(Fig 1G)**. While a significant NR-induced increase in cerebral NAD levels was detected at the group level, this effect was not uniform at the individual level. The magnitude of the cerebral NAD-increase showed high interindividual variation **(Fig 1C)**. Moreover, three participants showed no evidence of cerebral NAD response, despite a clear peripheral metabolic response, confirming treatment compliance and an impact on the NAD metabolome, in CSF, blood, and muscle. Thus, the variable cerebral NAD response observed by ^{31}P-MRS may reflect interindividual variability in cerebral penetration and/or cerebral NAD metabolism.

3) NR is associated with clinical improvement of PD: NR was associated with a significant decrease in the total MDS-UPDRS (I-III) score between visits (mean decrease: 2.33 ± 2.35; paired t-test: p = 0.017).

4) NR has a major impact on cerebral metabolism: ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), performed at baseline and 30 days of treatment, revealed that NR altered cerebral metabolic activity. The analysis revealed a significant ordinal trend pattern (i.e., metabolic network), which was represented by the first principal component (PC1), accounting for 20.6% of the variance in the paired data. This novel **NR-related metabolic pattern (NRRP)** was characterized by multiple regional metabolic changes, including bilateral metabolic reductions in the caudate and putamen, extending into the adjacent globus pallidus, and in the thalamus **(Fig 1D-E)**. Interestingly, the NRRP overlapped spatially with the Parkinson's Disease-Related Pattern (PDRP)[33], and changes in NRRP expression in the NR group resulted in partial normalization of the striatal and thalamic hypermetabolism **(Fig 1D)**, typically

characterizing the PD brain[33]. Furthermore, changes in NRRP expression in the NR group correlated significantly (r=-0.59, p = 0.026) with a decrease of the UPDRS ratings recorded at the time of PET **(Fig 1F)**. These results indicate that NR ameliorates the cerebral metabolic pattern of PD, and this is associated with significant clinical improvement.

5) NR has widespread metabolic and regulatory effects: Metabolomics revealed highly significant increase in NAD-related metabolites in blood, muscle and CSF **(Fig 1G)**, indicating that NR supplementation boosts NAD metabolism across tissues. Intriguingly, RNA-sequencing in blood and muscle biopsy showed a highly significant (FDR < 10^{-8}) upregulation of the mitochondrial, proteasomal and lysosomal pathways in the NR group. These findings indicate that NR supplementation increases both mitochondrial respiration and proteostasis – two hallmark pathogenic processes involved in PD[34]

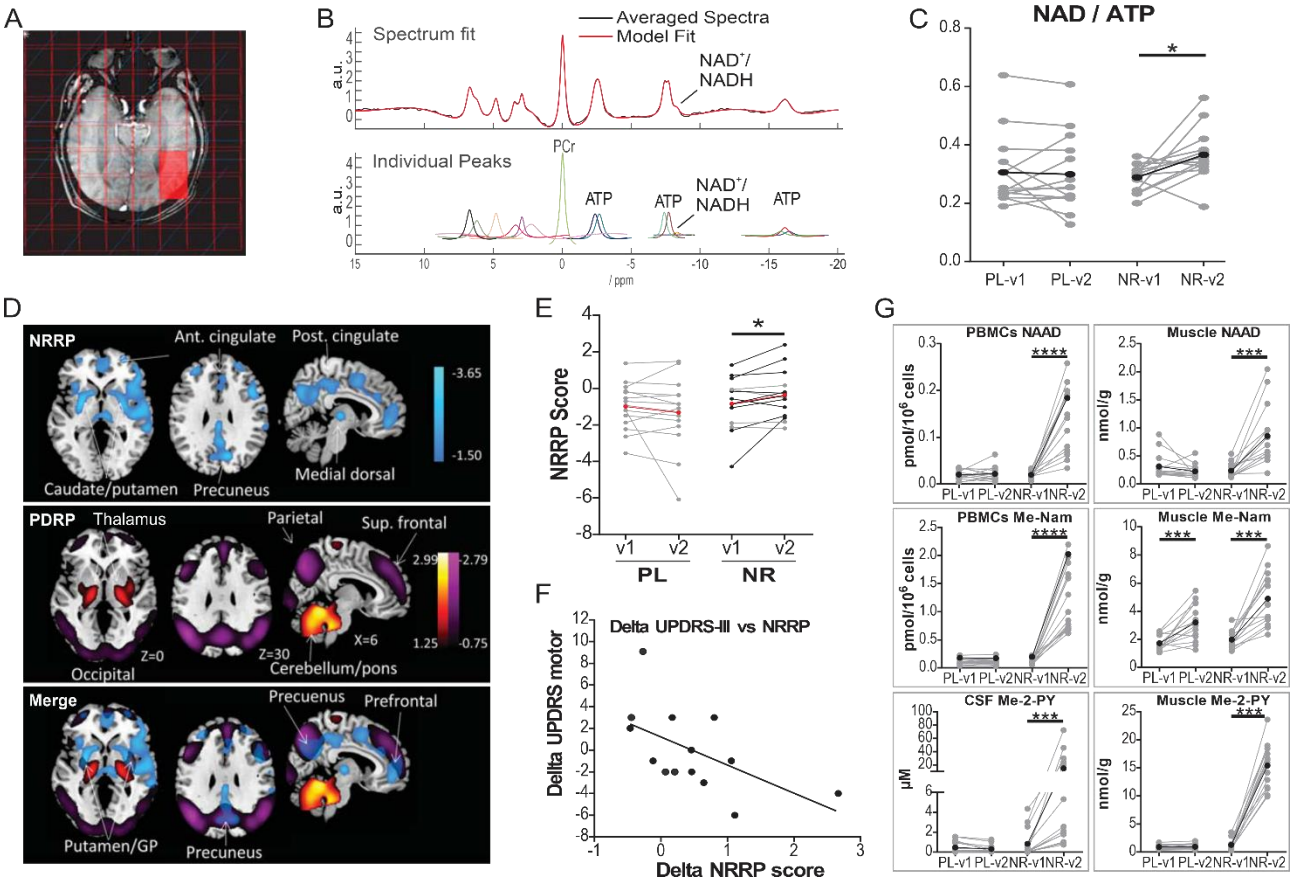

Fig 1. Results of the NADPARK trial. A-C: 31P-MRS was performed at baseline (v1) and after 30 days of treatment (v2). **A:** exemplary data from one subject showing voxel position. Spectra were acquired for each grid position. **B (top):** average processed spectra from multiple voxels (black) and the model fit (red). **B (bottom):** the model fit is composed of the convolution of all spectral contributions of a simulated dataset fitted to the experimental data. Arrow shows the NAD^+/NADH spectral peaks. PCr: phosphocreatine. **C:** comparison of cerebral NAD levels in the placebo (PL) and NR groups at baseline (v1) and visit-2 (v2). The Y-axis shows measured levels of NAD normalized to α-ATP (which remain unchanged and stable by the intervention). Individual subjects are indicated by dots. Connecting lines show the change between v1 and v2. The black points and lines show the mean of each group. The treatment group shows a highly significant increase in cerebral NAD levels (*paired t-test p = 0.016), whereas no difference is observed in the placebo group (paired t-test p = 0.75). **D: FDG-PET data** from all subjects in the NR-group, showing the mean NR-Related Pattern (NRRP, top panel), PD-related pattern (PRDP, middle panel), and the overlap of the two (bottom panel). NR partially ameliorates the striatal and thalamic hypermetabolism of PD. **E:** Between visit changes showing increased NRRP expression in the NR versus the placebo group. The red line indicates mean values before and after the treatment, black lines indicate individuals with a positive NAD response in the

MRS analysis, grey lines indicate individuals without an NAD response in the MRS (*p =0.027, permutation test, 1000 iterations). **F:** the NR-induced change in metabolic pattern (delta NRRP) shows a strong negative correlation (P<0.01) with the decrease in the UPDRS score (delta UPDRS). **G: Metabolomics in PBMCs, muscle, and CSF.** NR-induced metabolic changes include highly significant (p<<0.001 for all tests) increases in the acid form of NAD (NAAD), and nicotinamide (Nam) degradation products: methyl-Nam (Me-Nam) and the methyl pyridone (Me-2-PY).

II. The NR-SAFE study (ClinicalTrials.gov: NCT05344404)[21] is a phase I randomized, double blinded trial, aiming to assess the safety, tolerability, and bioavailability of NR in PD at an oral dose of 3000 mg daily. A total of 20 individuals with PD were randomized, in a 1:1 ratio, to NR 1500 mg x2/day or placebo for 30 days. The study was concluded in July 2022 and is currently in preparation. The main results are summarized below:

1) NR at a dose of 3000 mg daily is safe and well-tolerated: the treatment had excellent compliance, tolerability, and no signs of toxicity or clinically significant adverse effects in PD.

2) NR, 3000 mg daily, augments NAD-metabolism: oral NR intake at a dose of 3000 mg daily induced a potent (up to 5-fold) and highly significant augmentation of NAD^+ and $NADP^+$ levels, as well as a clear increase of the redox ratio (NAD^+/NADH) and the $NADP^+$/NADPH ratio (Fig. 2A).

3) NR, 3000 mg daily, is associated with clinical improvement of PD: the treatment was associated with a significant and substantial decrease in the total MDS-UPDRS (I-IV) score between visits (mean decrease 14 ± 13.7; paired t-test: P = 0.01). No significant change was seen in the placebo group (Fig. 2B). The UPDRS change (delta) in the NR-group was significantly higher than that of the placebo (t-test, P =0.02) (Fig. 2C).

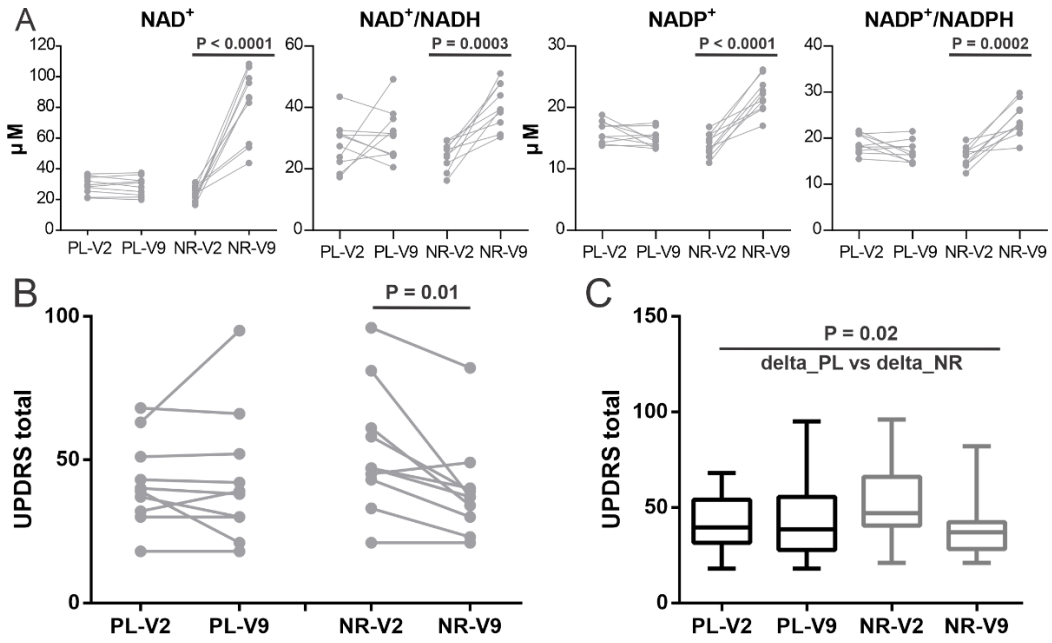

Fig 2. Results of the NR-SAFE trial. A: Metabolomics were performed in snap-frozen blood from the NR-SAFE participants at baseline (V2) and after 30 days of treatment (V9). Oral NR intake at a dose of 3000 mg daily induced a potent (up to 5-fold) and highly significant augmentation of NAD^+ and $NADP^+$ levels, as well as a clear increase of the redox ratio (NAD^+/NADH) and the $NADP^+$/NADPH ratio. P-values indicate the results of paired t-tests in the NR-group. There were no significant changes in the placebo group. **B:** Oral NR intake at a dose of 3000 mg daily was associated with a significant and substantial decrease in total MDS-UPDRS in the NR (mean decrease 14 ± 13.7; paired t-test: p = 0.01), but not in the placebo (mean decrease 1 ± 12.7; paired t-test: p = 0.81). **C:** At the group level, the change (delta) in total MDS-UPDRS in the NR group was significantly (t-test, P = 0.02) larger than that of the placebo group (B).

Key: V2: baseline; V9: after 30 days of treatment; NR: the group receiving NR 3000 mg daily; PL: the placebo group.

1.4 Rationale for the Study and Purpose

Our phase I trials (see section 1.3) showed that NR holds promise as a potential neuroprotective, disease-modifying therapy for PD, and that its effects are likely to be dose-dependent. Encouraged by these findings, this project aims to determine the optimal biological dose of NR in PD and to further explore its neuroprotective potential. The outcomes of this project will take us several steps closer to developing NR into a PD-drug, so that we may harness its full therapeutic potential and maximize its clinical benefit and impact. Specifically, the following knowledge gaps (KG) will be addressed by the N-DOSE study:

KG1 – Determine the Optimal Biological Dose (OBD) of NR in PD. We define the OBD of NR as the dose required to achieve maximal cerebral NAD increase (measured by 31P-MRS or CSF metabolomics), **or** maximal expression increase in the NRRP (measured by FDG-PET), **or** maximal proportion of MRS-responders, **in the absence of** unacceptable toxicity.
While our trials show that the treatment responses to NR in PD are clearly dose-dependent, the OBD of NR in PD remains undetermined. Based on the results of NR-SAFE, it is likely that improved biological and clinical responses can be achieved by escalating the dose. Moreover, the NR OBD may not be universal. NADPARK showed that the NR-mediated increase in cerebral NAD-levels, and accompanying metabolic and clinical response, are not universal and vary across individuals. The fact that all NR-recipients showed a robust metabolic response in blood, muscle and CSF, suggests that the variable cerebral NAD response may reflect interindividual variability in cerebral NAD metabolism (i.e., variation in the rate of NAD-synthesis or consumption). It is likely that such differences can be modulated by varying the substrate concentration (i.e., the intake dose of NR). This question is critical to address, so that NR-therapy can be correctly dosed and tailored to individual patients to achieve an optimal neurometabolic response.

KG2 – Confirm whether NR has a symptomatic clinical effect and assess its dose responsiveness. The NADPARK and NR-SAFE studies showed that NR was associated with a clinical improvement, in the form of UPDRS decrease, and this correlated significantly with the increase in cerebral NAD levels and change in the brain metabolic network (NRRP). Furthermore, the clinical improvement was more pronounced with 3000 mg NR in the NR-SAFE study, compared to 1000 mg in the NADPARK study. These findings suggest that NR may be ameliorating neuronal function in PD, resulting in symptom improvement. Confirming this effect and assessing its dose-dependence will allow us to: **1)** determine the optimal clinical dose of NR in PD, and **2)** account for symptomatic effects in neuroprotection trials.

KG3 – Determine the dose-dependence of the metabolic response to NR therapy. The NADPARK study showed that a dose of 1000 mg NR daily augmented the NAD metabolome in PBMC, muscle and CSF. The NR-SAFE study suggested that a dose of 3000 mg NR daily leads to a more potent augmentation of the NAD metabolome in blood. The relationship between NR dose and metabolic response needs to be further explored in order to determine optimal dosing regimens.

KG4 – Determine whether NR therapy enhance proteostasis in PD and characterize the dose dependence of this effect. Impaired proteostasis plays a central role in PD and other neurodegenerative disorders, including Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS). Our transcriptomic analyses in the NADPARK study indicated that NR therapy may enhance proteostasis by inducing the expression of both proteasomal and lysosomal pathways. If confirmed, this would suggest that NR targets

multiple major processes implicated in the pathophysiology of PD, including mitochondrial respiratory dysfunction, oxidative damage, lysosomal and proteasomal impairment, and neuroinflammation. Moreover, it is not known whether higher NR doses can induce stronger induction of proteostasis in PD.

KG5 – Determine whether NR therapy influences histone acetylation status and characterize the dose dependence of this effect. We have recently shown that genome-wide histone hyperacetylation and altered transcriptional regulation occur in the brain of individuals with PD[12]. Increasing neuronal NAD levels would boost the activity of the NAD-dependent histone deacetylases of the sirtuin family, potentially, ameliorating histone hyperacetylation in PD. It is currently unknown whether NR-therapy influences histone acetylation status in PD, and whether this effect is dose-dependent.

KG6 – Confirm that NR therapy decrease neuroinflammation and characterize the dose dependence of this effect. While it is known that NR has anti-inflammatory properties in peripheral tissues[24], the results of the NADPARK trial suggest it also downregulates multiple inflammatory cytokines in the central nervous system. If confirmed this would be of importance for PD and other neurodegenerative and neuroinflammatory disorders. Moreover, it is not known whether higher NR doses can induce stronger anti-inflammatory effects in PD.

KG7 – Determine whether NR therapy alter methylation metabolism and characterize any dose dependence of such an effect. In theory, NAD replenishment via NR administration could decrease/deplete the cellular methylation capacity. NR boosts the NAD-metabolome, leading to increased production of the degradation product nicotinamide (NAM), which is eliminated via methylation to MeNAM, Me-2-PY, and Me-4-PY, and excreted in the urine. Synthesis of Me-Nam requires the methyl-donor *S*-adenosylmethionine (SAM). This, in turn, could limit SAM availability for other essential methylation reactions, such as DNA and histone methylation, and neurotransmitter synthesis, including dopamine[35]. Thus, in theory, NR would cause an increased consumption of SAM, limiting methylation reactions and generating higher levels of homocystein. Such a phenomenon would be a particular concern for the ~60% of the population that carries MTHFR variants that reduce the efficiency of methylation. The NADPARK study showed no change in serum homocystein levels, or any other evidence of methylation depletion associated with NR 1000 mg daily. It is, however, unknown whether such effects may occur with higher NR doses.

KG8 – Determine how orally ingested NR interacts with the microbiome in PD. Current evidence suggests that the gut microbiome is involved in the pathogenesis of PD and that individuals with PD host a different microbiome composition compared to neurologically healthy individuals[36]. It is possible that NR therapy may beneficially affect the gut microbiome in PD restoring normal patterns. On the other hand, it is also possible that variation in the gut microbiome may affect local metabolism of NR and absorption in the bloodstream. These effects have not been studied.

To address these pertinent questions, we will conduct N-DOSE, a single-center randomized double-blinded placebo-controlled trial to assess the optimal biological dose for NR.

2 STUDY OBJECTIVES AND RELATED ENDPOINTS

DS-group refers to the dose-stable group, i.e. participants receiving NR 1000 mg daily for 3 months. DE-group refers to the dose-escalation group, i.e. participants receiving NR 1000 mg in an escalating dose with 1000 mg from baseline to week 4, 2000 mg from week 4 to week 8 and 3000 mg from week 8 to week 12. PL-group refers to the placebo group.

Objective		**Endpoint**
Primary	To compare the effect of orally administered nicotinamide riboside (NR), escalated to 1500 mg twice per day (3000 mg/day) in the dose-escalation group (DE-group) - versus stable dosing of 500 mg twice per day (1000 mg/day) in the dose-stable group (DS-group) on cerebral NAD-levels, at week 12.	Change in cerebral NAD/ATP-α ratio measured by 31 Phosphorus magnetic resonance spectroscopy (31P-MRS) in the posterior brain (encompassing the occipital, parietooccipital and posterior parts of the temporal cortex).
Secondary	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in cerebral NAD levels from baseline to weeks 4, 8 and 12.	Change in cerebral NAD/ATP-α ratio measured by 31 Phosphorus magnetic resonance spectroscopy (31P-MRS) in the posterior brain (encompassing the occipital, parietooccipital and posterior parts of the temporal cortex).
	To compare the effectiveness of orally administered nicotinamide riboside (NR) 1500 mg twice per day versus 500 mg twice per day in augmenting the NAD-metabolome in the central nervous system (CNS) at week 12.	Change in the cerebrospinal fluid (CSF) levels of NAD or other metabolites of the NAD metabolome*, measured by LC-MS.
Exploratory	**Neuroimaging**	
	To compare the effect of orally administered NR in the DE-group versus DS-group on the NR related metabolic pattern (NRRP) expression at week 12.	Change in NRRP expression, measured by FDG-PET.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in NRRP expression from baseline to weeks 4, 8 and 12.	Change in NRRP expression, measured by FDG-PET.
	To compare the effect of orally administered NR DE-group versus DS-group on the PD-related pattern (PDRP) expression at week 12.	Change in PDRP expression, measured by FDG-PET.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in PDRP expression from baseline to weeks 4, 8 and 12.	Change in PDRP expression, measured by FDG-PET.
	Metabolism & molecular markers	
	To compare the effect of orally administered NR in the DE-group versus DS-group on the NAD metabolome* in the blood, urine and central	Change in levels of NAD metabolites in blood, urine and CSF, measured by HPLC-MS and/or the NADMed method.

	nervous system (CNS) at week 12.	
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in the NAD metabolome* in blood and urine from baseline to weeks 4, 8 and 12.	Change in levels of NAD metabolites in blood and urine, measured by HPLC-MS and/or the NADMed method.
	To compare the effect of orally administered NR in the DE-group versus DS-group on serum and CSF inflammatory markers at week 12.	Change in inflammatory cytokines in serum and CSF, measured by ELISA.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in serum inflammatory markers from baseline to weeks 4, 8 and 12.	Change in inflammatory cytokines in serum, measured by ELISA.
	Clinical – motor & non motor symptom severity, quality of life	
	To compare the effect of orally administered NR in the DE-group versus DS-group on clinical severity of PD symptoms at week 12.	Change in the total MDS-UPDRS score in the ON-medication state.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and change in clinical severity of PD symptoms from baseline to weeks 4, 8 and 12.	Change in total MDS-UPDRS score in the ON-medication state.
	To compare the effect of orally administered NR in the DE-group versus DS-group on severity of non-motor symptoms of daily living in PD at week 12.	Change in the MDS-UPDRS part I score in the ON-medication state.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and change in severity of non-motor symptoms of daily living in PD from baseline to weeks 4, 8 and 12.	Change in the MDS-UPDRS part I score in the ON-medication state.
	To compare the effect of orally administered NR in the DE-group versus DS-group on severity of motor aspects of experiences of daily living in PD at week 12.	Change in the MDS-UPDRS part II score in the ON-medication state.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in severity of motor aspects of experiences of daily living in PD from baseline to weeks 4, 8 and 12.	Change in the MDS-UPDRS part II score in the ON-medication state.
	To compare the effect of orally administered NR in the DE-group versus DS-group on severity of PD motor symptoms at week 12.	Change in the MDS-UPDRS part III score in the ON-medication state.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in severity of PD motor symptoms from baseline to weeks 4, 8 and 12.	Change in the MDS-UPDRS part III score in the ON-medication state.
	To compare the effect of orally administered NR in the DE-group versus DS-group on severity PD motor complications at week 12.	Change in the MDS-UPDRS part IV score in the ON-medication state.

	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in severity of PD motor complications from baseline to weeks 4, 8 and 12.	Change in the MDS-UPDRS part IV score in the ON-medication state.
	To compare the effect of orally administered NR in the DE-group versus DS-group on clinical severity of PD non-motor symptoms at week 12.	Change in the total MDS-NMS score.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in clinical severity of PD non-motor symptoms from baseline to weeks 4, 8 and 12.	Change in the total MDS-NMS score.
	To compare the effect of orally administered NR in the DE-group versus DS-group on clinical severity of gastrointestinal non-motor dysfunction in PD at week 12.	Change in the modified GIDS-PD score.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in clinical severity of gastrointestinal non-motor dysfunction in PD from baseline to weeks 4, 8 and 12.	Change in the modified GIDS-PD score.
	To compare the effect of orally administered NR in the DE-group versus DS-group on cognition at week 12.	Change in the MoCA score.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in cognition from baseline to weeks 4, 8 and 12.	Change in the MoCA score.
	To compare the effect of orally administered NR in the DE-group versus DS-group on quality of life in PD at week 12.	Change in the EQ-5D-5L score.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in quality of life in PD from baseline to weeks 4, 8 and 12.	Change in the EQ-5D-5L score.
	Hypothesis-generating or resource-dependent endpoints (may be reported in follow-up or secondary publications).	
	To compare the effect of orally administered NR in the DE-group versus DS-group on gene expression at week 12.	Change in gene expression, measured by RNA sequencing (RNAseq).
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in gene expression from baseline to weeks 4, 8 and 12.	Change in gene expression, measured by RNA sequencing (RNAseq).
	To compare the effect of orally administered NR in the DE-group versus DS-group on protein expression at week 12.	Change in protein levels, measured by LC-MS.

	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in protein expression from baseline to weeks 4, 8 and 12.	Change in protein levels, measured by LC-MS.
	To compare the effect of orally administered NR in the DE-group versus DS-group on serum and CSF inflammatory markers at week 12.	Change in inflammatory cytokines in serum and CSF, measured by ELISA.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in serum inflammatory markers from baseline to weeks 4, 8 and 12.	Change in inflammatory cytokines in serum, measured by ELISA.
	To compare the effect of orally administered NR in the DE-group versus DS-group on histone acetylation in PD at week 12.	Change in histone panacetylation, measured by immunoblotting.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in histone acetylation in PD from baseline to weeks 4, 8 and 12.	Change in histone panacetylation, measured by immunoblotting.
	To compare the effect of orally administered NR in the DE-group versus DS-group on H3K27 and H4K16 histone acetylation in PD at week 12.	Changes in levels of H3K27 and H4K16 acetylation, measured by immunoblotting.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in on H3K27 and H4K16 histone acetylation in PD from baseline to weeks 4, 8 and 12.	Changes in levels of H3K27 and H4K16 acetylation, measured by immunoblotting.
	To compare the effect of orally administered NR in the DE-group versus DS-group on the genomic distribution of H3K27 and H4K16 histone acetylation in PD at week 12.	Change in the genomic distribution of H3K27 and H4K16 acetylation, measured by chromatin immunoprecipitation sequencing (ChIPseq).
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in the genomic distribution of H3K27 and H4K16 histone acetylation in PD from baseline to weeks 4, 8 and 12.	Change in the genomic distribution of H3K27 and H4K16 acetylation, measured by chromatin immunoprecipitation sequencing (ChIPseq).
	To compare the effect of orally administered NR in the DE-group versus DS-group on folate and one-carbon metabolism in PD at week 12.	Change in folate and one-carbon metabolites in blood and CSF, measured by HPLC-MS.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in folate and one-carbon metabolism in PD from baseline to weeks 4, 8 and 12.	Change in folate and one-carbon metabolites in blood, measured by HPLC-MS.
	To compare the effect of orally administered NR in the DE-group versus DS-group on methyl donors in PD at week 12.	Change in methyl-donors (e.g., SAM), measured by HPLC-MS, in the blood and/or CSF.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg	Change in methyl-donors (e.g., SAM), measured by HPLC-MS, in the blood.

	per day) and changes in methyl-donors in PD from baseline to weeks 4, 8 and 12.	
	To compare the effect of orally administered NR in the DE-group versus DS-group on DNA methylation at week 12.	Change in level and genomic distribution of DNA methylation, measured by Illumina Infinium MethylationEpic kit.
	To assess the dose-response relationship between NR dose (1000 mg, 2000 mg, 3000 mg per day) and changes in methyl-donors in PD from baseline to weeks 4, 8 and 12.	Change in level and genomic distribution of DNA methylation, measured by Illumina Infinium MethylationEpic kit.
	To compare the effect of orally administered NR in the DE-group versus DS-group on synthesis of neurotransmitters in PD at week 12.	Change in neurotransmitters in CSF, measured by HPLC-MS.
	Determine whether NR-therapy affects the gut microbiome in a dose-responsive manner at week 12.	Change in gut microbiome composition, measured by metagenomics in fecal samples.
	To compare the effect of orally administered NR in the DE-group versus DS-group on the gut metabolome at week 12.	Change in fecal metabolomics, measured by LC-MS in fecal samples.
	To compare the effect of orally administered NR in the DE-group versus DS-group on the sense of smell at week 12.	Change in sense of smell, measured by B-SIT score.
Safety	To determine the safety and tolerability of NR at a dose of 1000 mg, 2000 mg, and 3000 mg per day in PD.	Number and severity of adverse events from baseline to week 12 across treatment groups and NR dose levels.

***The NAD metabolome is comprised of:** Nicotinamide adenine dinucleotide oxidized (NAD^+), Nicotinamide adenine dinucleotide reduced (NADH), NAD^+/NADH ratio, total NAD (sum of NAD^+ and NADH), Nicotinamide adenine dinucleotide phosphate oxidized ($NADP^+$), Nicotinamide adenine dinucleotide phosphate reduced (NADPH), $NADP^+$/NADPH ratio, total NADP (sum of $NADP^+$ and NADPH, 1-methyl nicotinamide (Me-Nam), nicotinic acid-adenine dinucleotide (NAAD), N1-methyl-2-pyridone-5-carboxamide (Me-2-PY), Nicotinamide (Nam), Nicotinamide N-oxide (Nam N-oxide), ADP-ribose (ADPR), Nicotinic acid riboside (NAR), Nicotinamide riboside (NR), Nicotinamide mononucleotide (NMN), Nicotinic acid (NA).

2.1 Primary Endpoint Measure

Change in cerebral NAD level, measured by ^{31}P-MRS.

^{31}P-MRS assesses the levels of key-energy metabolites in the brain, including NAD, ATP, free inorganic phosphate (Pi), and phosphocreatine, and others, as previously shown[18,37]. Using this method, we will assess total brain NAD levels normalized to ATP-α levels (i.e., the NAD/ATP-α ratio) in the posterior brain - encompassing the occipital, parietooccipital and posterior parts of the temporal cortex.

2.2 Secondary Endpoint Measure

Change in the CSF level of NAD or other metabolites of the NAD metabolome in CSF, measured by HPLC-MS.

Using **high performance liquid chromatography mass spectrometry (HPLC-MS)**, we will measure the NAD metabolome in CSF, including the following specific measures: Nicotinamide adenine dinucleotide oxidized (NAD^+), Nicotinamide adenine dinucleotide reduced (NADH), NAD^+/NADH ratio, total NAD (sum

of NAD^+ and NADH), Nicotinamide adenine dinucleotide phosphate oxidized ($NADP^+$), Nicotinamide adenine dinucleotide phosphate reduced (NADPH), $NADP^+$/NADPH ratio, total NADP (sum of $NADP^+$ and NADPH, 1-methyl nicotinamide (Me-Nam), nicotinic acid-adenine dinucleotide (NAAD), N1-methyl-2-pyridone-5-carboxamide (Me-2-PY), Nicotinamide (Nam), Nicotinamide N-oxide (Nam N-oxide), ADP-ribose (ADPR), Nicotinic acid riboside (NAR), Nicotinamide riboside (NR), Nicotinamide mononucleotide (NMN), Nicotinic acid (NA).

2.3 Exploratory Endpoint Measures

Change in the following parameters listed below:

NR related pattern (NRRP), an ordinal trend pattern (i.e., metabolic network), associated with NR treatment identified in the NADPARK study[18], measured by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET).

PD related pattern (PDRP), an ordinal trend pattern (i.e., metabolic network), associated with PD[33], measured by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET).

The International Parkinson and Movement Disorder Society – Non-Motor Rating Scale (MDS-NMS)[38], a 52 item scale that assesses the frequency and severity of non-motor symptoms in PD across 13 non-motor domains. The MDS-NMS consists of two parts: the Total MDSS-NMS (range 0-832) and the MDS-NMS Non-Motor Fluctuations (NMF) Subscale to assess changes in non-motor symptoms in relation to the timing of anti-parkinsonian medication (range 0-128). Each item in each scale is scored according to frequency from 0 to 4 and severity from 0 to 4. Each item's frequency is then multiplied by its severity to calcultate the item scorer. A low score indicates a good outcome, higher scores indicate a poorer outcome.

The International Parkinson's disease and movement disorders society unified Parkinson's disease rating scale (MDS-UPDRS)[39] is a scale assessing clinical impairment and disability in PD. It consists of 4 parts. Part I assesses non-motor experiences of daily living and has 2 components IA and IB (Range 0-52). Part IA comprises 6 questions assessed by the examiner (Range 0-24). Part IB comprises 7 questions completed by the participants (Range 0-28). Part II assesses motor experiences of daily living (Range 0-52). It comprises 13 questions completed by the participant. Part III evaluates motor severity and contains 33 scores based on 18 items, which are assessed by the rater during clinical examination (Range 0-132). Part IV assesses motor complications, which comprises 6 questions assessed by the examiner (Range 0-24). For each question a numeric score is assigned between 0-4, where 0 = Normal, 1 = Slight, 2 = Mild, 3 = Moderate, 4 = Severe. MDS-UPDRS Total Score equals the sum of parts I, II, III and IV (Range 0-260). A higher score indicates more severe symptoms of PD.

MDS-UPDRS part I is a scale assessing non-motor experiences of daily living and has 2 components (Range 0-52). Part IA comprises 6 questions assessed by the examiner (Range 0-24). Part IB comprises 7 questions completed by the participants (Range 0-28). A higher score indicated more severe symptoms. This will be assessed in the ON medication state.

MDS-UPDRS part II assesses motor experiences of daily living (Range 0-52). It comprises 13 questions completed by the participant. A higher score indicated more severe symptoms. This will be assessed in the ON medication state.

MDS-UPDRS part III evaluates motor severity and contains 33 scores based on 18 items, which are assessed by the rater during clinical examination (Range 0-132). For each question a numeric score is assigned between 0-4, where 0 = Normal, 1 = Slight, 2 = Mild, 3 = Moderate, 4 = Severe. A higher score

indicated more severe symptoms. This will be assessed in the ON medication state.

MDS-UPDRS part IV evaluates motor complications and contains 6 questions assessed by the examiner (Range 0-24). For each question a numeric score is assigned between 0-4, where 0 = Normal, 1 = Slight, 2 = Mild, 3 = Moderate, 4 = Severe. A higher score indicated more severe symptoms. This will be assessed in the ON medication state.

The International Parkinson and Movement Disorder Society Gastrointestinal Dysfunction Scale in Parkinson's Disease (mGIDS-PD)[40] modified*. The following version of GIDS-PD has been modified by permission and license from MDS for use in the N-DOSE trial. The modifications in this version are that the timeframe for all questions has been reduced from six months to one month. Part 1b has also been omitted from the scale. A low score indicates a good outcome, higher scores indicate a poorer outcome. The range is 0 to 108 points. The scale consists of two main parts: Section 1 -12, which are counted as a scale. Section 1a, and sections A – F, which are anamnestic and do not count towards the scale score.

MoCA[41] is a validated global measure of cognitive ability. This will be assessed in the ON medication state.

EQ-5D-5L[42] is a 5 item questionnaire and visual analogue scale that allows calculation of quality adjusted life years (QALY) to enable health economic analyses to be performed. The questionnaire covers 5 domains with scores 0 to 4. A low score indicates a good outcome, higher scores indicate a poorer outcome. The EQ VAS score in mm is a general assessment from the participants perspective of how good their health is, from 0 to 100. A low score indicates a poor outcome, a high value indicates a better outcome.

NAD metabolome. Using liquid chromatography mass spectrometry (HPLC-MS) and/or the NADMed method, we will measure the NAD metabolome in whole blood (and/or PBMCs), CSF and urine including the following specific measures: Nicotinamide adenine dinucleotide oxidized (NAD^+), Nicotinamide adenine dinucleotide reduced (NADH), NAD^+/NADH ratio, total NAD (sum of NAD^+ and NADH), Nicotinamide adenine dinucleotide phosphate oxidized ($NADP^+$), Nicotinamide adenine dinucleotide phosphate reduced (NADPH), $NADP^+$/NADPH ratio, total NADP (sum of $NADP^+$ and NADPH, 1-methyl nicotinamide (Me-Nam), nicotinic acid-adenine dinucleotide (NAAD), N1-methyl-2-pyridone-5-carboxamide (Me-2-PY), Nicotinamide (Nam), Nicotinamide N-oxide (Nam N-oxide), ADP-ribose (ADPR), Nicotinic acid riboside (NAR), Nicotinamide riboside (NR), Nicotinamide mononucleotide (NMN), Nicotinic acid (NA).

Gene and protein expression levels in PBMC, measured by RNA sequencing (RNAseq) and proteomics (HPLC-MS), respectively.

Levels of inflammatory cytokines in serum and CSF, measured using enzyme-linked immunosorbent essay (ELISA).

Levels of histone panacetylation, and levels and genomic distribution of H3K27 and H4K16 acetylation in PBMC, measured by immunoblotting and chromatin immunoprecipitation sequencing (ChIPseq).

Levels of methyl-donors (e.g., SAM) in blood and/or CSF, measured by HPLC-MS.

Levels of neurotransmitters in CSF, measured by HPLC-MS.

Levels of one carbon metabolism metabolites, measured by HPLC-MS metabolomics in PBMC and CSF.

Levels and genomic distribution of DNA methylation, measured by the Illumina Infinium

MethylationEPIC Kit.

Gut microbiome composition, assessed by metagenomics in fecal samples.

Fecal metabolomics, including fatty acid profiling, assessed by HPLC-MS in fecal samples**.**

Brief Smell Identification Test (B-SIT) assesses olfaction. It consists of 12 items with 4 alternatives, from which the participant attempts to identify the correct smell. It is performed by the participant under supervision of the investigator. Not available for all participants as this was added as an exploratory outcome during the trial. A low score indicates a poor outcome, higher scores indicate a better outcome. The range for the total score is 0 to 12 points.

3 OVERALL STUDY DESIGN

This is a single-center, phase II, double blinded, randomized, placebo-controlled dose-optimization study.

Study Period	Estimated date of first patient enrolled: 28.11.2022
	Anticipated recruitment period: 28.11.2022 – 20.01.2025B
	Estimated date of last patient completed: 22.04.2025
Treatment Duration:	12 weeks.

3.1 Study design

N-DOSE is a single-center, phase II, double blinded, randomized, placebo-controlled dose-optimization clinical trial with a dose escalation design. Patients with PD (n = 80) who fulfil participation criteria (see section 4) will be randomized (1:1:2) into one of three groups: **1) The placebo group** (PL-group, n = 20) will receive placebo for the duration of the study. **2) The NR 1000 mg group** (DS-group, n=20) will receive NR 1000 mg (500 mg x 2) per day for the duration of the study. **3) The NR dose escalation group** (DE-group, n=40) will receive first 1000 mg (500 mg x 2) NR per day for 30 days, then 2000 mg (1000 mg x 2) NR per day for 30 days, and finally 3000 mg (1500 mg x 2) NR per day for 30 days (Fig. 3). The selected dose range is within safety limits for healthy humans (see section 1.3). After eligibility screening, eligible participants will be randomly assigned to one of three study groups and assessed at baseline (Visit-1, V1) and three more visits (Visit-2, Visit-3 and Visit-4; V2, V3, V4) spaced 30 days apart (Fig. 3). Participants and investigators will be blinded to treatment group. Participants will be followed for a total of 90 days. All participants will be recruited from the Neuro-SysMed Center, at the department of Neurology, Haukeland University Hospital (HUS).

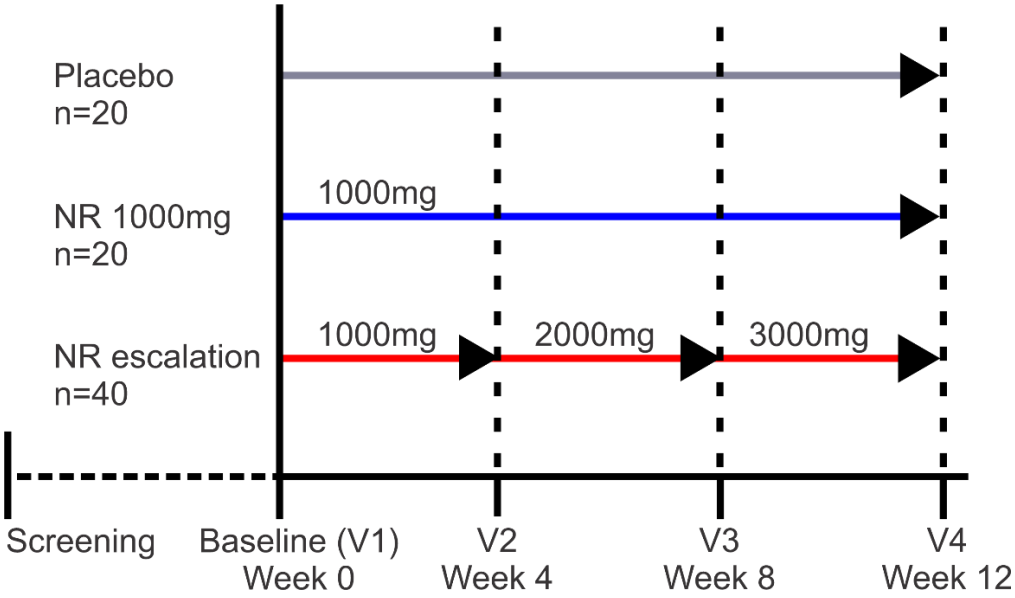

Figure 3. N-DOSE design. A total of 80 patients will be recruited in three arms. Patients will be assessed at baseline (V1) and three additional visits, at 4 (V2), 8 (V3) and 12 (V4) weeks.

4 STUDY POPULATION

4.1 Selection of Study Population

The study will include individuals ≥ 40 years with a clinically established diagnosis of PD according to the MDS criteria[43], and Hoehn and Yahr score < 4 (see full list of eligibility criteria below). Participants from all of Norway will be recruited at the department of Neurology, Haukeland University Hospital.

4.2 Number of Patients

A total of n=80 patients will be included in this study and randomized to placebo (PL-group, n=20), NR 500 mg twice per day (DS-group, n=20), or NR escalating dose (DE-group, n=40), starting at 500 mg twice per day, increasing to 1000 mg twice per day,, and finally increasing to 1500 mg twice per day.

4.3 Inclusion Criteria

The following condition must apply to the prospective patient at screening prior to receiving study agent:

- Clinically established diagnosis of PD according to the MDS criteria.
- 123I-Ioflupane dopamine transporter imaging (DAT-scan) or 18-F-FDOPA positron emission tomography imaging (18F-FDOPA PET) confirming nigrostriatal degeneration.
- Hoehn and Yahr score < 4 at enrolment.
- Age ≥ 40 years at the time of enrollment.
- Able to undergo lumbar punction.
- Able to undergo MRI

4.4 Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

- Dementia or other neurodegenerative disorder at baseline visit.
- Diagnosed with atypical parkinsonism (PSP, MSA, CBD) or vascular parkinsonism.
- Any psychiatric disorder that would interfere with compliance in the study.
- Metabolic, neoplastic, or other physically or mentally debilitating disorder at baseline visit.
- Use of high dose vitamin B3 supplementation within 30 days of enrollment.

5 TREATMENT

For this study NR (Niagen®, Chromadex) is defined as the Investigational Product(s) (IP). IP includes also active comparator and placebo.

5.1 Drug Identity, Supply and Storage

NR (Niagen®, Chromadex) and placebo will be manufactured and provided from Chromadex. Both NR and Placebo will be prepared as identical capsules. The drug has marketing consent in Norway but is not registered by Statens legemiddelverk (SLV)/Direktoratet for medisinske produkter (DMP) as medical drug but as a supplement. The NR and placebo have a 1-year expiry date. Both the NR and placebo will be stored in room temperature with temperature <25 degrees (according to instructions given by Chromadex).

5.2 Dosage and Drug Administration

Each NR capsule contains 250 mg. To keep the study fully blinded, all participants will receive the same number of daily capsules irrespective of which treatment group they belong to. To achieve this, NR capsules will be combined with placebo capsules as necessary (see below):

- Patients in the NR 1000mg group will administer orally [2 NR capsules (250mg) + 4 placebo capsules] x 2 times daily (1000mg NR daily in total).
- Patients in the NR dose escalation group will administer orally the following doses:
    - Weeks 0-4: [2 NR capsules (500mg) + 4 placebo capsules] x 2 times daily (1000mg NR daily in total).
    - Weeks 5-8: [4 NR capsules (1000mg) + 2 placebo capsules] x 2 times daily (2000mg daily total).
    - Weeks 9-12: [6 NR capsules (1500mg) + 0 placebo capsules] x 2 times daily (3000mg daily total).
- The placebo group will administer orally [6 placebo capsules] x 2 times daily.

There is no specified time of day the dosages should be taken, only that they should be taken with about 12 hours apart if possible. If a dose is missed, the patient can take the missed dose as soon as it is remembered, provided it is shorter time to the missed dose than the next scheduled dose. There are no restrictions with respect to combining the dose with other medication and/or food.

The study medication is to be taken every day during the treatment period, and must be taken prior to study visits.

5.3 Duration of Therapy

Therapy duration for the study is 3 months (12 weeks).

5.4 Dopaminergic therapy during Screening and Treatment period

Eligible and consenting men and women with PD will be given optimal dopaminergic therapy, as indicated by their clinical disease. All and any form of dopaminergic therapy formally approved in Norway may be used. Patients who do not use dopaminergic therapy are eligible, provided that they have a clinically established diagnosis of PD according to the MDS criteria. The treatment regimen will be optimized, if necessary, and will then be frozen and remain unchanged for the study period (3 months):

- For patients who are already on dopaminergic therapy, the regimen may be adjusted, if necessary, to optimal clinical effect. Adjustment may involve change in dose, formulation, or drug. When adjustment of the dopaminergic regimen is undertaken, treatment efficacy will be assessed upon reexamination by physical or telephone consultation, until optimal effect or exclusion. Once the treatment regimen is deemed optimal, it will be frozen and remain unchanged for the study period (3 months).
- Newly diagnosed and/or treatment naïve patients will be given dopaminergic treatment if- and as appropriate based on clinical indication. The treatment will be titrated to optimal effect. When adjustment of the dopaminergic regimen is undertaken, treatment efficacy will be assessed upon reexamination by physical or telephone consultation, until optimal effect or exclusion. Once the treatment regimen is deemed optimal, it will be frozen and remain unchanged for the study period (3 months).
- Patients who do not use dopaminergic therapy are eligible, provided that they have a clinically established diagnosis of PD according to the MDS criteria.

If adverse effects occur due to the dopaminergic therapy after enrollment, the treatment will be adjusted according to good clinical practice. All patients will be enrolled to the main study within 3 months after the last screening if inclusion/exclusion criteria are fulfilled.
At the end of study visit (month 3), the physician determines whether the patient is still adequately treated for his/her parkinsonism with their current dopaminergic treatment.

5.5 Concomitant Medication

Dopaminergic therapy will be given as described in section 5.4. above.

In addition, the patient should not take any vitamin B3 supplements for the duration of the study.

There are no other restrictions on any other use of medications. All patients should use medications prescribed prior to enrollment in the study. There are no restrictions with respect to starting new medications that are necessary for the patient.

All concomitant medication (incl. vitamins with the exception of vitamin B3, herbal preparation and other “over-the-counter” drugs) used by the patient will be recorded in the patient’s file and CRF.

5.6 Subject Compliance

Patient compliance will be determined based on self-report at study visits. A pill count of remaining medication will be performed when providing new study medication and at the end of the study.

5.7 Drug Accountability

The responsible site personnel will confirm receipt of study drug and will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return, and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures. Study drugs are stored locally at the study site and distributed by the study nurse upon registration in CRF. Remaining study drug is returned for pill count.

5.8 Drug Labeling

The investigational product will have a label permanently affixed to the outside and will be labeled according with ICH GCP and national regulations, stating that the material is for clinical trial / investigational use only and should be kept out of reach of children.

Label will include:

- Kit number
- Study number (CRF number)
- Expiration date

5.9 Subject Numbering

At the screening visit, each patient will be sequentially allocated a study identification number by the CRF (i.e., the registration code of the patient in the CRF). The study identification should be as follows: YYYY, where YYYY is the chronological enrolled subject number (e.g., 0001, 0002, etc.). For example: 002 (patient number 002). The next enrolled patient is registered as 003.
The subjects will be identified by this study identification number for the remainder of the study. Once a patient number has been assigned, no attempt will be made to use that number again. If a patient number is allocated incorrectly, no attempt will be made to remedy the error once study treatment has been dispensed. Any replacement patients will be given the next patient number in the sequence.

6 STUDY PROCEDURES

6.1 Flow Chart

Table 1. Trial flow chart

	Screening Period		**Treatment Period Study Visit**			
Event	**First Screening**	**Subsequent/ last screening**	**Visit-1 Baseline**	**Visit-2**	**Visit-3**	**Visit-4**
Time			**Week 1**	**Week 4**	**Week 8**	**Week 12**
Informed consent	X					
Informed consent biobank	X					
MDS Clinical diagnosis Criteria (MDS CDC)	X					
Inclusion/exclusion Evaluation	X		X			
Medical history[1]	X		X			
Physical Examination[2]	X		X	X	X	X

	Screening Period		Treatment Period Study Visit			
Event	**First Screening**	**Subsequent/ last screening**	**Visit-1 Baseline**	**Visit-2**	**Visit-3**	**Visit-4**
General neurological examination	X					
Body height			X			
Vital signs[3]			X	X	X	X
Body weight and BMI			X	X	X	X
Record of concomitant medication[9]	X		X	X	X	X
Hoehn and Yahr score	X		X	X	X	X
DAT-Scan or 18F-FDOPA PET[4]	X					
31P-MRS & 1H-MRS of the brain			X	X	X	X
FDG-PET of the brain			X	X	X	X
MDS-UPDRS (I-IV)			X	X	X	X
MDS-NMS			X	X	X	X
MoCA			X	X	X	X
EQ-5L			X	X	X	X
GIDS-PD			X	X	X	X
B-SIT			X			X
Dietary registration (3 days)			X			X
Routine blood tests[5]			X	X	X	X
Blood collection for biobanking[6]			X	X	X	X
Cerebrospinal fluid collection			X			X
Fecal sample collection			X			X
Urine sample collection			X	X	X	X
Treatment dispensation[7]			X	X	X	
Dopaminergic treatment stable[8]	X	X				X
Adverse event				X	X	X

Superscripts refer to the specifications below.

Specifications (details in section

1. Medical history includes: family history of neurological illness (what and who), family history of PD (what and who), smoking history (period, pack-years), first PD symptoms, months since first PD symptoms, occurrence and duration of REM sleep disorder symptoms, occurrence and duration of loss of smell.
2. Heart and lung auscultation, abdominal palpation, any other examination dictated by patient's condition/symptoms
3. Blood pressure, pulse, temperature
4. DAT-Scan or 18F-FDOPA PET must have been performed prior to the Baseline Study Visit.
5. CRP, ALAT, ASAT, GT, bilirubin, ALP, creatinine, urea, RBC, Hb, WBC with differential, platelets, CK, FT4, TSH, B12, folic acid, homocysteine, methylmalonic acid, sodium, potassium, glucose. Women of childbearing potential will also have a pregnancy test performed.
6. EDTA blood, snap-frozen EDTA blood, platelets, serum (see lab manual for details).
7. To ensure correct dosages during dose escalation and if necessary to resupply.

8. The patient must be on a stable dopaminergic treatment regimen. When the patient is on a stable dopaminergic treatment, the screening is over, and the patient can be included in the study. The dopaminergic treatments are listed in section 5.4. There should not be more than 3 months from the last screening to the baseline visit.
9. Record of concomitant medication: in addition to all drugs used by the patient, the type of dopaminergic medication used and the time points in the day at which each dose is taken must be registered.

6.2 By Visit

6.2.1 **Screening Visits/ Before start of Investigational Product (IP)**

The first screening visit aims to determine if the patient is eligible to be included in the study. A full physical examination and anamnestic medical history is performed. If the patient fulfills the inclusion/exclusion criteria and gives informed consent, dopaminergic treatment is initiated/adjusted as described in the treatment flowchart in section 5.4.
If the patient is optimally treated with dopaminergic treatment and fulfills the inclusion/exclusion criteria, then the patient is deemed ready for enrolment and may be referred to MRI and PET. If changes are made to the dopaminergic treatment, then the subject is contacted by phone after 2-6 weeks to assess if the treatment is optimal. If the patient is optimally treated, this dopaminergic treatment is frozen for the remainder of the study and the patient is referred to MRI and PET and called in for the baseline study visit (week 0 study visit). The patient should at screening be advised to stop using any Vit B3 supplement to fulfill inclusion criteria. There should not be more than 3 months from the last screening to baseline visit.

Screening checklist:

1. Patient signs informed consent for N-DOSE
2. Patient signs informed consent for consent for storage and analysis of biological material ("Samtykke for lagring av biologisk material i biobank for demens og aldring")
3. Physical examination (general neurological examination) at first screening
4. MDS clinical diagnosis Criteria
5. Record current use of medication. Advise to stop any use of vit B3 supplements
6. Introduce/adjust dopaminergic treatment as described in section 5.4.
7. If the patient is ready for enrollment, they are referred to baseline study visit (including MRI and PET).
8. The patient is given the 3-day dietary registration form along with instructions on how to fill it out and deliver to the study nurse at baseline.
9. Register when the patient takes their dopaminergic medication (dose and time of the day).
10. Patient is asked to note the time of dopaminergic therapy intake on the morning of each visit
11. Visits should be planned so that the patient is at the Department at a time permitting the MDS-UPDRS to be conducted within **no less than 15min and no more than 2 hours** after the last intake of dopaminergic medication.
12. MDS-UPDRS must be conducted at the same interval from the last dopaminergic therapy dose on every visit (+/- 30min)

6.2.2 **Baseline/Week 0**

1. Investigator verifies the informed consent for the study.

2. Investigator verifies anamnestic information gathered at screening, current use of medication and medical history.
3. Investigator verifies fulfillment of inclusion and exclusion criteria.
4. The study identification number is assigned (see section 5.9).
5. Study medication is dispensed to the subject by the study nurse and the patient is reminded to take the study medication every day including the morning of each visit.
6. Register the time the patient took dopaminergic medication on the morning of the visit as well as the type and dose of the medication.
7. The following clinical examination are performed by the study nurse or investigator (see flowchart in section 6.1):
    - Vital signs
    - Body weight and BMI
    - MDS CDC
    - MDS-UPDRS: section 1&2 by study nurse/investigator, section 3&4 by investigator
    - MDS-NMS
    - MoCA
    - EQ-5L
    - GIDS-PD
8. Routine blood tests are done (see flowchart in section 6.1)
9. Samples for biobanking are taken (see flowchart in section 6.1):
    - EDTA whole blood
    - Snap-frozen whole blood
    - PAXgene blood for RNA
    - Serum
    - Fecal sample
    - Urine sample
    - Cerebrospinal fluid
10. Imaging is conducted
    - 31P-MRS & 1H-MRS
    - FDG-PET
11. All data gathered during study visits is either written into the electronic journal or filled out in paper format with appropriate date and signatures. Each patient will have their own folder with gathered clinical data. The clinical tests (MDS-UPDRS, MDS-NMS, MoCA, MDS CDC, EQ-5L, GIDS-PD) are recorded in paper format.
12. The patient is given the 3-day dietary registration form along with instructions on how to fill it out and deliver it to the study nurse at the next visit.
13. Patient is reminded to note the time of dopaminergic therapy intake on the morning of the next visit
14. Next visit should be planned so that the patient is at the Department at a time permitting the MDS-UPDRS to be conducted within **no less than 15min and no more than 2 hours** after the last intake of dopaminergic medication.
15. MDS-UPDRS must be conducted at the same interval from the last dopaminergic therapy dose on every visit (+/- 30min)
16. B-SIT is performed by either the study nurse or investigator (see flowchart in section 6.1).

6.2.3 During treatment (visits 2-4)

- Should the patient need replenishing of study medication, it will be logistically handled by the study nurse.
- On visit 2 points 5-11 and 13-15 from section 6.2.2 are repeated.
-
- On visit 3, points 5-15 from section 6.2.2 are repeated.

6.2.4 *End* of study (Visit 4)

- The patient brings with them the remaining study medication which is gathered by the study nurse for a pill count. Clinical examinations are performed as listed in section 6.1.
- Points 6-11 from section 6.2.2 are repeated.
- B-SIT is performed by either the study nurse or investigator (see flowchart in section 6.1).
- At the end of the study visit, consider changes in the dopaminergic treatment.

6.3 Criteria for Patient Discontinuation

Patients may be discontinued from study treatment and assessments at any time. Discontinuation and the reason for discontinuation (withdrawn from the study) will be registered. Specific reasons for discontinuing a patient for this study are:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment.
- Safety reasons as judged by the Principal Investigator.
- Incorrect enrolment, i.e., the patient does not meet the required inclusion/exclusion criteria for the study.
- Deterioration in the patient's condition which in the opinion of the Principal Investigator warrants study medication discontinuation (to be records as an AE or under Investigator Discretion).

6.4 Procedures for Discontinuation

6.4.1 Patient Discontinuation

Patients who are withdrawn from the study before the start of treatment will be replaced. Withdrawn patients are not followed up.

6.4.2 Trial Discontinuation

The whole trial may be discontinued at the discretion of the PI or the sponsor in the event of any of the following:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration.
- Medical or ethical reasons affecting the continued performance of the trial.
- Difficulties in the recruitment of patients.

The sponsor and principal investigator will inform all investigators and the Ethics Committees of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety and Ethics Committees will be informed within 15 days.

7 ASSESSMENTS

The schedule of assessments is indicated in Section 6 (see section 6.1, Flow Chart).

7.1 Safety and Tolerability Assessments

Safety will be monitored by AE registration at every visit. Significant findings that are present prior to the signing of informed consent must be included in the relevant medical history/ current medical condition page of the e-CRF. For details on AE collection and reporting, refer to Section 8.

7.2 Clinical Assessments

1. **Medical history:**
   Performed by: investigator
   a. Family history of neurological illness:
      i. Who
      ii. Which illness.
   b. Family history of PD:
      i. Who
      ii. Was the diagnosis certain, probable or possible
   c. Smoking history:
      i. Active smoker, previous smoker, or never smoker?
      ii. Cigarettes smoked daily (on average)
      iii. Duration of smoking (years)
      iv. Pack-years (pack-years = cigarettes smoked daily / 20 x years of smoking)
   d. First PD symptoms:
      i. Which symptoms: tremor, bradykinesia, gait abnormality, rigidity, loss of smell, other (if other = free text comment).
      ii. History of REM sleep behavior disorder (RBD)
         1. RBD: yes/no
         2. If yes – duration (i.e., for how long has the subject had it)
   e. Presence and duration of olfactory changes:
      i. Complete loss of smell: yes/no?
      ii. Decreased sense of smell?
      iii. If yes – duration (i.e., for how long has the subject had it)
2. **Vital signs:**
   Performed by: study nurse
   a. Blood pressure.
   b. Pulse.
   c. Temperature.
3. **Body metrics:**
   Performed by: study nurse
   a. Body weight.
   b. Height.
   c. BMI.
4. **Physical examination:**

Performed by: investigator

a. Heart and lung auscultation.
    i. Heart: normal / findings (free field)
    ii. Lungs: normal / findings (free field)
b. Abdominal palpation: normal / findings (free field)
c. Any other examination dictated by patient's condition/symptoms: free field.

5. **General neurological examination**

Performed by: investigator

a. Register any findings not related to the subject's parkinsonism: free field.

6. **Clinical scales & registrations:**

Performed by: see individual tests below

a. MDS CDC:
   Performed by: investigator
b. MDS-UPDRS I-IV
    i. NB! The exact time MDS-UPDRS is assessed must be registered in the eCRF.
   Performed by: section 1&2 by study nurse/investigator, section 3&4 by investigator
c. MDS-NMS:
   Performed by: Investigator or study nurse
d. MoCA:
   Performed by: study nurse
e. EQ-5L:
   Performed by: study nurse
f. GIDS-PD:
   Performed by: study nurse
g. 3-day dietary record:
   Performed by: self-filled by the patient

7.3 Routine Laboratory Tests

These will include: CRP, ALAT, ASAT, GT, bilirubin, ALP, creatinine, urea, RBC, Hb, WBC with differential, platelets, CK, FT4, TSH, B12, folic acid, homocysteine, methylmalonic acid, sodium, potassium, glucose. Women of childbearing potential will also have a pregnancy test performed.
Laboratory tests and biosampling are listed and described in detail in Appendix A.

7.4 Imaging studies

1. **DAT-scan**, performed according to standard clinical routine, will confirm the presence of nigrostriatal degeneration.
2. **31P-MRS** (CSI, multinuclear coil – 15 min) will be conducted on a 3T Biograph mMR MR-PET scanner (Siemens Healthcare, Germany) to assess the intracerebral concentration of NAD, as we have done before (Fig 1A-C).
3. **FDG-PET** imaging will be performed on the same MR-PET scanner and in the same session, to assess the metabolic response to NR treatment, as we have previously shown (Fig 1D-E). Following standard preprocessing protocols and spatial normalization, the NRRP will be assessed using ordinal trends/canonical variates analysis (OrT/CVA), a supervised form of principal component analysis (PCA)33. This multivariate approach is designed to detect and quantify regional covariance patterns

(i.e., metabolic networks) for which expression values (i.e., subject scores) increase or decrease with treatment in all or most of the subjects34–38.

The MRI protocol is also summarized in Appendix B.

7.5 Molecular analyses

1) Metabolomics analyses will be performed in snap-frozen blood, PBMC, and CSF, using liquid chromatography-mass spectrometry (LC-MS) as described[44]. Absolute metabolite concentrations will be determined using in house standards. We will assess the entire NAD-metabolome, and key-metabolites involved in the Krebs' cycle, fatty acid beta-oxidation, and methylation reactions (e.g., SAM, homocysteine, folate).

2) Gene and protein expression. The transcriptome will be mapped in PBMC and/or PAXgene samples by RNA-sequencing, using ribosomal depletion and sequencing at 125 bp paired-end and 100 million read pairs per sample, as we have previously described[45]. Quantitative proteomics will be performed in PBMC, muscle and CSF, using TMT (Tandem Mass Tags) labeling and mass spectrometry (LC-MS/MS Q-Exactive HF).

3) Histone acetylation profiling. As in our previous work[12], we will first assess quantitative changes in global histone acetylation status in PBMC and muscle, by immunoblotting with a pan-acetyl-lysin antibody. Next, acetylation levels of specific lysine residues (e.g., H3K27 and H4K16) will be assessed with targeted immunoblotting. Finally, genome-wide changes in the acetylation status of histone lysine residues found to be quantitatively altered by the treatment, will be assessed by chromatin-immunoprecipitation sequencing (ChIP-Seq)[12].

4) Inflammatory cytokine concentration will be determined in CSF using ELISA as in the NADPARK trial[18].

5) DNA methylation will be mapped in PBMC and/or snap-frozen blood using the Illumina Infinium Epic Chip.

6) Neurotransmitter levels. Monoamine levels will be determined in the CSF using HPLC-MS.

7) Gut microbiome. Using fecal samples, we will assess the microbiota profile (i.e., estimates of composition and abundance) by metagenomics, and function by microbial metabolomics. Metagenomics analyses will comprise 16S-rRNA sequencing-based count of operational taxonomic units (OTUs), Illumina NovaSeq short-read sequencing, and long-read sequencing by MinION technology. For microbial metabolomics, feces will be analyzed for short-chained fatty acids (SCFA) and, if feasible, NAD-related metabolites.

8 SAFETY MONITORING AND REPORTING

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE). Each patient will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious. The methods for collection of safety data are described below.

8.1 Definitions

8.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.
An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.
The term AE is used to include both serious and non-serious AEs.
If an abnormal laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory result/vital sign should be considered as additional information that must be collected on the relevant CRF.
Only intensity 2 and 3 is registered as AE in eCRF, see section 8.3. An AE has to interfere with everyday life to be of intensity 2 or 3.

8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment is to be exercised in deciding on the seriousness of a case. Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the listed outcomes in the definitions above. In such situations, or in doubtful cases, the case should be considered as serious. Hospitalization for administrative reasons (for observation or social reasons) is allowed at the investigator's discretion and will not qualify as serious unless there is an associated adverse event warranting hospitalization.

8.2 Time Period for Reporting AE and SAE

Recording AE and SAEs will begin after baseline (week 0) and continue to be monitored and registered throughout the duration of the study up until 7 days after last study visit.
During the course of the study all AEs and SAEs will be proactively followed up for each patient; events should be followed up to resolution, unless the event is considered by the investigator to be unlikely to resolve due to the underlying disease. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

8.3 Recording of Adverse Events

If the patient has experienced adverse event(s), the investigator will record the following information in the e-CRF:

- The nature of the event(s) will be described by the investigator in precise standard medical terminology (i.e., not necessarily the exact words used by the patient).
- The duration of the event will be described in terms of event onset date and event ended data.

The intensity of the adverse event: Only intensity grade 2 and 3 is registered as AE in eCRF .

Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: **1. Mild**: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities, and or requires clinical or diagnostic observations. **2. Moderate**: An event that causes sufficient discomfort to interfere with normal everyday activities, and or requires medical intervention. **3. Severe**: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

The Causal relationship of the event to the study medication will be assessed as one of the following:

- **Unrelated:** There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AE.
- **Unlikely:** There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE.
- **Possible:** There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear.
- **Probable:** There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.
- **Definite:** There is a reasonable causal relationship between the investigational product and the AE.

- It will be recorded in the eCRF the outcome of the adverse event, the action taken and whether the event is resolved or still ongoing.

- It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 8.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but is not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

8.4 Reporting Procedure

8.4.1 AEs and SAEs

All adverse events and serious adverse events that should be reported as defined in section 8.1.1 will be recorded in the patient's CRF.

SAEs must be reported by the investigator to the sponsor, (coordinating investigator: Haakon Berven or PI Charalampos Tzoulis, see contact information) within 24 hours after the site has gained knowledge of the SAE. Every SAE must be documented by the investigator on the SAE pages to be found in e-CRF. The initial report shall promptly be followed by detailed, written reports if necessary. The initial and follow-up reports shall identify the trial subjects by unique code numbers assigned to the latter.

The sponsor keeps detailed records of all SAEs reported by the investigators and performs an evaluation with respect to seriousness, causality and expectedness.

8.5 Clinical Study Report

The adverse events and serious adverse events occurring during the study will be discussed in both the main results and the safety evaluation part of the Clinical Study Report.

9 DATA MANAGEMENT AND MONITORING

9.1 Electronic - Case Report Forms (e-CRFs)

The study nurse/investigator will enter the data required by the protocol into the electronic Case report forms (e-CRF) online. The electronical CRF that will be used is Viedoc. The Investigator is responsible for assuring that data entered into the e-CRF for his/her patient is complete, accurate, and that entry is performed in a timely manner. The signature of the investigator will attest to the accuracy of the data on each CRF. If any assessments are omitted, the reason for such omissions will be noted on the e-CRFs.

At study visit the following source date should be registered either on paper or hospital records. See section 6.1 and 6.2 for when the relevant information is gathered. This data will then be transferred to eCRF by the study nurse/investigator.

- That the patient is participating in the study, e.g., by including the enrollment number and the study code or other such study identification
- Date when Informed Consent was obtained from the patient and statement that patient received a copy of the signed and dated Informed Consent
- Results of all assessments confirming a patient's eligibility for the study
- Diseases (relevant past and current with date; both the disease studied and others, as relevant)
- Medical history
- Laboratory data
- Results of clinical assessments performed during the study
- Treatment given
- Non-Serious Adverse Events and Serious Adverse Events (if any) including causality assessments
- Date of, and reason for, discontinuation from study treatment
- Date of, and reason for, withdrawal from study

9.2 Study Monitoring

The investigator will be visited on a regular basis by the Clinical Study Monitor, who will check the following:

- Informed consent process
- Reporting of adverse events and all other safety data

- Adherence to protocol
- Maintenance of required regulatory documents
- Study Supply accountability log
- Data completion on the e-CRFs including source data verification (SDV).

The monitor will review the relevant e-CRFs for accuracy and completeness and will ask the site staff to adjust any discrepancies as required.

When the responsible study monitor has checked and verified the e-CRFs, the data will be entered into a computer database at the Haukeland University hospital scientific server for further handling and statistical evaluation.

Sponsor's representatives (e.g., monitors, auditors) and/or competent authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study may be required.

9.3 Confidentiality

The investigator shall arrange for the secure retention of the patient identification and the code list. Patient files shall be kept for the maximum period of time permitted by the hospital. The study documentation (e-CRFs, Site File etc) shall be retained and stored during the study and for 5 years after study closure. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

9.4 Database management

- Access to study after the study completion is granted by Charalampos Tzoulis.
- Data for each patient will be recorded on the eCRF. Data collection must be completed for each patient who signs an informed consent form and receives at least one dose of study treatment.
- eCRFs will be designed and produced by the Investigator and should be completed in accordance with instructions. The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information will be transcribed directly into the eCRFs using a secure internet connection. The eCRFs should be filled out completely by the Investigator or designee as stated on the delegation of responsibilities form.
- The eCRFs must be reviewed, signed and dated by the Investigator.
- Data entered into the eCRF will be validated as defined in the data validation plan. Validation includes, but is not limited to, validity checks (e.g., range checks), consistency checks and customized checks (logical checks between variables to ensure that study data are accurately reported) for eCRF data and external data (e.g., laboratory data). A majority of edit checks will be triggered during data entry and will therefore facilitate efficient 'point of entry' data cleaning.
- Data management personnel will perform both manual eCRF review and review of additional electronic edit checks to ensure that the data are complete, consistent and reasonable. The electronic edit checks will run continually throughout the course of the study and the issues will be reviewed manually online to determine what action needs to be taken.
- Manual queries may be added to the system by clinical data management or study monitor. Clinical data managers and study monitors are able to remotely and proactively monitor the patient eCRFs to improve data quality.
- Pharmacokinetic data will be transferred electronically into the study database. Discrepancies

will be queried to the site and/or the laboratory until the electronic data and the database are reconciled.

- All updates to queried data will be made by authorized study center personnel only and all modifications to the database will be recorded in an audit trail. Once all the queries have been resolved, eCRFs will be locked by password protection. Any changes to locked eCRFs will be approved by the Investigator.
- Once the full set of eCRFs have been completed and locked, the Sponsor will authorize database lock and all electronic data will be sent to the designated statistician for analysis. Subsequent changes to the database will then be made only by written agreement.
- Adverse events and medical history will be coded from the verbatim description (Investigator term). Prior and concomitant medications and therapies will be coded according to the World Health Organization drug code.

10 STATISTICAL METHODS AND DATA ANALYSIS

10.1 Determination of Sample Size

Our primary null hypothesis (H_0) is that the NR-induced increases in cerebral NAD levels (measured by 31P-MRS) are not dose-responsive. The alternative hypothesis (H_A) is that this measure is dose responsive. In the NADPARK study, all three measures showed a highly significant increase in the group receiving 1000 mg NR (n = 15) compared to the placebo group (n = 15). In the NADPARK study[46], treatment with 1000mg of NR led to an increase in cerebral NAD-levels by a factor of 1.27 from baseline in the treatment group, whereas the change in the placebo group was negligible at -0.43%. Under the H_A, we assume that cerebral NAD levels will increase in a linear fashion in the 2000 mg NR and 3000 mg NR groups, respectively. Based on these assumptions and given a type I error rate of 5% ($\alpha = 0.05$) and a type II error rate of 10% ($\beta = 0.1$, power = 90%), we estimated that a sample size of 30 individuals will be required in the dose escalation group. Accounting for drop-out and statistical safety margin, we estimate that the study requires 40 subjects in this group.

For the secondary and exploratory outcomes, we assume that the metabolomic, transcriptomic and inflammatory cytokine analyses will have sufficient power, since they produced very large effect sizes and highly significant results in the NADPARK study with 15 individuals per group. Since no pilot data exists for the proteomic and epigenomic analyses, these will be exploratory in nature. However, in our previous experience, a sample size of 20 per group should be sufficient to detect treatment-induced differences of biological relevance.

10.2 Randomization

Randomization is done by e-CRF upon enrollment to the study. Participants will be randomized into one of three groups (Placebo, NR 1000 mg for the duration of the study, NR dose escalation group).

10.3 Population for Analysis

Intention to treat (ITT)/Full analysis set (FAS) population: All participants, regardless of protocol adherence.

The Safety Analysis Set (SAS) will include all patients having received at least one study treatment infusion after randomisation.

The Per Protocol Analysis Set (PPS) will include all randomized patients meeting the study eligibility criteria and with no major protocol deviations affecting the treatment efficacy.

The following are pre-defined major protocol deviations regarded to affect the efficacy of the intervention:

- Entering the trial when the eligibility criteria should have prevented trial entry.
- Discontinuation of intervention prior to 84 ± 7 days.
- Major change in concomitant anti-Parkinson medication.
- Received or used other intervention than allocated.
- Adherence to allocated treatment below 85%.
- Visit date interval larger than 28 ± 7 days between individual visits (i.e.: V1 and V2, V2 and V3 and V3 and V4)*.
- Visit date interval larger than 84 ± 7 days from V1 to V4*.
- Not fasting before neuroimaging.

*Due to updated findings from a pharmacokinetic study (ClinicalTrials.gov, NCT: NCT05698771, in revision) that NAD levels increase and reach a plateau within 1-2 weeks of NR treatment both in healthy individuals and persons with Parkinson's disease. A 3 week period should therefore be sufficient to assess the effects of increasing NR dosage.

10.4 Planned analyses

All statistical analyses will take place after the completion of the study. All randomized patients will be included in the primary analyses and sensitivity analyses will be carried out comparing results from the ITT, SAS and PPS data sets. In the case of missing assessments, the subject will be included if possible.

The ***primary analysis*** of the primary endpoint will be performed using analysis of covariance (ANCOVA) between the dose stable (DS-group) and dose escalation group (DS-group), i.e. the regression of NAD levels measured by ^{31}P-MRS at week 12 depending on randomization group and adjusted for ^{31}P-MRS at baseline. No additional adjustments/covariates will be used. As this is the single primary outcome, alpha will be set at 0.05. No correction for multiple testing will be performed.

The ***secondary analysis*** of the primary endpoint will be the comparison of change over time from baseline to week 4, week 8 and week 12, between the DE-group and the DS-group. This will be assessed using a linear mixed model (LME), i.e. NAD (^{31}P-MRS) at weeks 4,8 and 12 depending on randomization group, time and their interaction adjusted for random individual intercept.

The ***primary analysis*** of the secondary endpoint will be performed using ANCOVA between the dose stable (DS-group) and dose escalation group (DS-group), i.e. the regression of NAD or NAD metabolite levels measured by HPLC-MS at week 12 depending on randomization group and adjusted for NAD or NAD metabolite at baseline. No additional adjustments/covariates will be used.

The analysis of exploratory endpoints will be performed in a similar manner as for the primary and secondary endpoints. ANCOVA will be used to compare endpoints at week 12, and LME will be used to compare change from baseline to week 4, week 8 and week 12.

In addition, for PET analyses, changes in network scores with treatment will be evaluated for each group separately using permutation tests. Relationships between network values, brain NAD levels and MDS-UPDRS motor ratings or between treatment-related changes in these variables will be evaluated using Pearson's product-moment correlations, whereas Spearman rank-order correlation coefficients will be computed for non-normally distributed variables.

Omics data will undergo rigorous quality control and filtering according to established best practice procedures, as we have previously described[12,45,47,48]. The between visit change in this data will be assessed by a pairwise comparison between each NR group and the placebo group, using linear models with appropriate covariates as we have previously described[12,45,47,48]. Comparison of adverse events and abnormal laboratory test results between the treatment and placebo groups will be analyzed descriptively.

Further details for the analysis are outlined in the statistical analysis plan (SAP) for the trial, and we refer the reader to this document.

10.5 Statistical Analysis

Dependent variable

Primary analysis:

- Cerebral NAD levels (measured by ^{31}P-MRS)

Secondary, exploratory and safety analyses:

- Adverse events, categorized as either moderate or severe.
- Levels of CSF NAD and NAD-metabolites (measured by LC-MS).
- Levels of NRRP expression (measured by FDG-PET)
- Levels of PDRP expression (measured by FDG-PET)
- Routine blood tests
- Total MDS-UPDRS
- MDS-UPDRS Part I
- MDS-UPDRS Part II
- MDS-UPDRS Part III
- MDS-UPDRS Part IV
- MDS-NMS
- MoCA
- GIDS-PD
- EQ-5D-5L
- Levels of NAD-related and other metabolites in PBMC, frozen blood, urine and CSF
- Expression of RNA and protein of genes and pathways involved in proteasomal and lysosomal biogenesis and function.
- Histone panacetylation levels
- Levels of specific lysine residues H3K27 and H4K16 acetylation

- Genome-wide distribution of histone lysine residues found to be quantitatively altered by the treatment (measured by ChIP-Seq).
- Level of inflammatory cytokines in patient serum and CSF.
- Gene and protein expression levels in PAXgene blood.
- Levels of one carbon metabolism metabolites, measured by HPLC-MS metabolomics in PBMC and CSF.
- Levels of monoamine neurotransmitters in CSF.
- Levels and genomic distribution of DNA methylation.
- Gut microbiome composition.
- Fecal metabolomics, including fatty acid levels.
- Sense of smell, measured by B-SIT.

Statistical hypothesis

Primary analysis:

- Our primary null hypothesis (H_0) is that the NR-induced increases in cerebral NAD levels (measured by ^{31}P-MRS) is not dose-responsive. The alternative hypothesis (H_A) is that this increase is dose responsive.

Secondary analysis:

- Mean change between the NR dose escalation arm and NR 1000 mg arm for the dependent variables mentioned above.
- Mean change between and within the NR dose escalation arm, NR 1000 mg arm and placebo arm for the dependent variables mentioned above.

11 STUDY MANAGEMENT

11.1 Investigator Delegation Procedure

The principal investigator is responsible for making and updating a “delegation of tasks” listing all the involved co-workers and their role in the project. He will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

11.2 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations.
All significant protocol deviations will be recorded and reported in the Case Report Form (CRF).

11.3 Study Amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to and the Ethics Committee according to EU and national regulations.

11.4 Audit and Inspections

Authorized representatives of the Ethics Committee may visit the center to perform inspections, including source data verification. Likewise, the representatives from the sponsor may visit the center to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-

related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (ICH GCP), and any applicable regulatory requirements. The principal investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

12 ETHICAL AND REGULATORY REQUIREMENTS

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

12.1 Ethics Committee Approval

Application to REK has been submitted. The investigator is responsible for informing the ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

12.2 Other Regulatory Approvals

Statens legemiddelverket (SLV)/Direktoratet for medisinske produkter (DMP) has deemed that the project is not a clinical trial due to the fact that NR is not classified as a drug, but as a nutritional supplement.

12.3 Informed Consent Procedure

All subjects will be presented verbally and with written informed consent to be signed prior to enrollment to the study. The informed consent will be presented at the first screening. Informed consent will be handled according to GCP principles. A copy of the informed consent will be given to the subject.

12.4 Subject Identification

Upon entry in screening, each subject is given a patient study number, this study number is used for the remainder of the study. The Patient study number is in the format XXYYY where XX is the study site number and YYY is the patient ID number.

The investigator is responsible for keeping a list of all patients (who have received study treatment or undergone any study specific procedure) including patient's date of birth and personal number, full names and last known addresses.

The patients will be identified in the CRFs by the patient study number and initials.

13 TRIAL SPONSORSHIP AND FINANCING

Research Council of Norway (RCN), Neuro-SysMed, (ES633272) 2020-2028

14 TRIAL INSURANCE

The Patients are insured by the government through the "Norsk Pasientskade Erstatning" (NPE).

15 PUBLICATION POLICY

Upon study completion and finalization of the study report the results of this study will either be submitted for publication and/or posted in a publicly accessible database of clinical study results.

The results of this study will also be submitted to the Ethics Committee according to EU and national regulations.

All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors.

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17 LIST OF APPENDICES

A. Lab Manual

B. Imaging Manual

C. Clinical Rating Scales

APPENDIX A

LABORATORY MANUAL FOR N-DOSE

Helse Bergen, Haukeland University Hospital

Protocol:
N-DOSE

REK Number:

N-DOSE SAFE: A randomized, double blind, dose optimization trial of nicotinamide riboside in Parkinson's disease.

STANDARD OPERATING PROCEDURE (SOP) FOR SAMPLING AND PREPARATION OF BIOLOGICAL MATERIAL (LAB MANUAL)

Project Management Committee for the study

Charalampos Tzoulis

Haakon Berven

1 GENERAL INFORMATION

The purpose of this document is to give an overview of the biological material collected for biobanking in the N-DOSE clinical trial. At different time points during the clinical trial the following biological samples are collected, processed and stored based on standard operating procedures: whole blood, serum, plasma, PBMCs, blood cells. The samples are stored at Biobank Haukeland and at the Neuro-SysMed Center.

In the following chapters you will find a detailed description of how to collect, prepare, and store samples at HUS. It is critically important that the samples are prepared correctly and standardized, and that all deviations from the protocol are documented. This information will be registered in LabVantage when the Biobank Information system is in operation and at the Neuro-SysMed Center.

2 HEMATOLOGY, BIOCHEMISTRY, HORMONE, SEROLOGY AND SAFETY LABORATORY PARAMETERS

This chapter describes the biological material that should be collected for hematology, biochemistry, hormone and serology analyses and for serum hCG pregnancy test. The collection should be done as specified in the Flow Chart. The local study site laboratory will be used for the analyses of these components, as indicated in the Study Protocol. Protocols for collection of biological material for research and biobanking are described in Chapter 3 and 4.

Flow chart					**TUBES**
Visits	**V1 / Baseline**	**V2**	**V3**	**V4**	
Week	**0**	**4**	**8**	**12**	
Routine:					
hCG[1]	X				
CRP	X	X	X	X	
ALAT	X	X	X	X	
ASAT	X	X	X	X	
GT	X	X	X	X	
Bilirubin	X	X	X	X	
ALP	X	X	X	X	
Creatinine	X	X	X	X	
Urea	X	X	X	X	
RBC	X	X	X	X	
Hb	X	X	X	X	
WBC with differential	X	X	X	X	
Platelets	X	X	X	X	
CK	X	X	X	X	
FT4	X	X	X	X	
TSH	X	X	X	X	
B12	X	X	X	X	
Folic acid	X	X	X	X	
homocysteine	X	X	X	X	
Methylmalonic acid	X	X	X	X	
Sodium	X	X	X	X	
Potassium	X	X	X	X	
Glucose	X	X	X	X	
Biobank:					
EDTA whole blood	X				FluidX, 0,7ml, 8 aliquotes
Snap-frozen whole blood	X	X	X	X	
PAXgene blood for RNA	X	X	X	X	PAXgene tubes
Platelets	X	X	X	X	
Serum	X	X	X	X	FluidX, 0,7ml, 8 aliquotes
Fecal sample	X			X	
Urine sample	X	X	X	X	
Cerebrospinal fluid	X			X	

2.1.1 Safety laboratory (blood)

All safety laboratory parameters will be collected at the timepoints as indicated in the Flow Chart (page 47), and include hematology, liver enzymes/parameters, clinical chemistry, thyroid status. The samples will be analyzed at the local laboratory at the study site. The respective reference ranges must be provided to the central study administration for uploading into the eCRF.

3 SAMPLING FOR BIOBANK AND RESEARCH

3.1 Mandatory research and biobank samples

Chapter 3.1 gives an overview of all mandatory samples collected for research and biobanking. The sample processing protocols are in Chapter 4.

3.1.1 Whole blood EDTA

EDTA blood will be collected at HUS

3.1.2 Whole blood EDTA – snap-frozen

Snap-frozen EDTA blood will be collected at HUS

3.1.3 RNA PAXgene tubes

Blood in PAXgene tubes for RNA extraction will be collected at HUS

3.1.4 Whole blood for Serum

Serum will be collected at HUS

3.1.5 Platelets

Platelets will be collected at HUS

3.1.6 Cerebrospinal fluid (CSF)

CSF will be collected at HUS

3.1.7 Feces

Feces will be collected at HUS

3.1.8 Urine

Urine will be collected at HUS

4 SAMPLE PROCESSING AND STORAGE

4.1 Whole blood (EDTA): standard

Performed at: HUS

Material and instrumentation:

Item	How many	Supplier	Cat no	Comment
VACUETTE® TUBE 2 ml K2E K2EDTA	2	Greiner Bio-One International	454024	
0.7 ml FluidX tubes	8	Pedro Consulting	68-0702-11N	
Pipettes & tips				
Barcode reader				
-80°C freezer		Study center		

Collection, preparation and storage:

1. Collect whole blood into Vacuette tubes for EDTA blood
2. Aliquot 500 µL blood into 8 x 0.7 ml FluidX tubes.
3. Freeze the aliquots at -80°C within 60 min after sample collection.
4. Use the barcode reader for registration of the sample and log all deviations on the same registration form.
5. Sample aliquots are stored at -80C and shipped on dry ice in the original FluidX boxes (x 48 tubes).
6. Samples must **never** be allowed to warm or thaw except from when to be used in analyses. Any deviation from this must be **registered**. The number and date of thawing an aliquot for analyses must be registered.

Contact person for biosampling and laboratory preparation:
Siri Hinteregger, MBF

Contact person for Biobank:
Hilde Kristin Garberg

FluidX tubes

FluidX tubes box (x48)

4.2 Whole blood (EDTA): snap-frozen

Performed at: HUS

Snap-frozen whole blood will be used for the analysis of NAD+. NAD degrades very rapidly after sample collection and the concern is that measurements in any sample that requires extensive processing may not prove reliable.

Material and instrumentation:

Item	How many	Supplier	Cat no	Comment
VACUETTE® TUBE 2 ml K2E K2EDTA	1	Greiner Bio-One International	454024	
Screw cap micro tubes, 0.5 ml, sterile	8	Sarstedt	72.730.006	
Multi dispenser pipette & tips				
Liquid nitrogen in a thermos				
-80°C freezer		Study center		
Timer				

NB! The time from blood drawing (i.e. moment the blood starts flowing into the tube) and freezing MUST be 2 min!

Collection, preparation and storage:

1. Print labels. For one patient: 8x
2. Mark 8 x 0.5 ml micro tubes with labels
3. Laboratory technician must be next to the patient at the blood drawing with all equipment ready.
4. Laboratory technicians must wear gloves and a lab coat.
5. Collect whole blood into the Vacuette tube.
6. **START THE TIMER when blood starts flowing into the tube.**
7. Gently invert the EDTA tube at least 10 times. **DO NOT SHAKE**
8. Aliquot 8 x 200 µl of blood from the 2 ml EDTA tube into 8 x 0.5 ml micro tubes (easiest using a multi dispenser pipette).
9. Close micro tubes
10. **When the timer shows 2min:** immerse all the micro tubes simultaneously in liquid nitrogen.
11. Transfer the frozen EDTA-aliquots -80^{o}C freezer for storage.
12. Sample aliquots are stored at -80C in freezer-compatible cardboard or plastic storage boxes.
13. Samples are shipped on dry ice.
14. Samples must **never** be allowed to warm or thaw except from when to be used in analyses. Any deviation from this must be **registered**. The number and date of thawing an aliquot for analyses must be registered.

If the 2 min interval is not respected – still collect the samples but register the time interval.

Responsible: Hanne Linda Nakkestad

4.3 RNA PAXgene tubes

Performed at: HUS

Rationale:
The Paxgene Blood RNA collection system is intended for the purification of intracellular RNA from whole blood and is optimized for the stabilization of 4.8 x10e6 – 1.1 x 10e7 leukocytes/ml. This protocol describes the collection of whole blood in Paxgene RNA tubes from Qiagen for long-term storage at -80° C.

Important: Paxgene collection tubes **must** be at room temperature prior to collection. Follow standard procedure for venipuncture for tubes with stabilizing agents e.g., butterfly collection

Material and instrumentation:

- PAXgene blood RNA tubes (PreAnalytix, Cat. No. 762165)
- BD Vacutainer SafetyLok Blood collection set (BD, Cat. No. 367281) or similar Butterfly and safety lock or similar
- Sample labels capable of storage at -80 °C
- Phlebotomy materials: Tourniquet, alcohol swabs, gauze
- Barcode reader
- -80°C freezer

Collection, preparation, storage and shipment:
Before starting, ensure PAXgene tubes are at ambient temperature and labeled appropriately with temperature resistant labels. Draw PAXgene tubes last, after other blood tubes. If the PAXgene tubes are the only tubes, draw a small amount of blood into a discard tube.

1. Using the Blood Collection set, collect blood into the PAXgene tube using standard venipuncture techniques. Ensure that the donor's arm is in a downward position, and that the PAXgene tube is **held vertically** below the donor's arm.
2. Collect 2.5 ml of blood into each PAXgene tube. so that the tube gets filled with **exactly** 2.5 ml blood. This is essential so that the final concentration of the reagents will be correct. If PAXgene is the first sample to be taken, collect some blood in another tube first, to get rid of the air in the collection system, so that the PAXgene tube gets exactly 2.5 ml blood.
3. Allow at least 10 s for the blood draw to occur and ensure that blood has stopped flowing into the tube before removing the needle from the tube.
4. Immediately after blood collection mix the tube by gentle inversion (180°) 10 times
5. Temporarily store the PAXgene upright at RT for between **2-24 hrs**.
6. Temporarily store the PAXGene tube for at least **24 hrs** at -20°C
7. After at least 24 hrs at -20°C, move the PAXgene tube for **long-term storage at -80 °C**
8. Sample aliquots are stored at -80C in freezer-compatible cardboard or plastic storage boxes.
9. Samples are shipped on dry ice.
10. Samples must **never** be allowed to warm or thaw except from when to be used in analyses. Any deviation from this must be **registered**.

Responsible:

Contact person for biosampling and laboratory preparation: Siri Hinteregger, MBF
Contact person for Biobank: Hilde Kristin Garberg

4.4 Serum for biobanking

Performed at: HUS

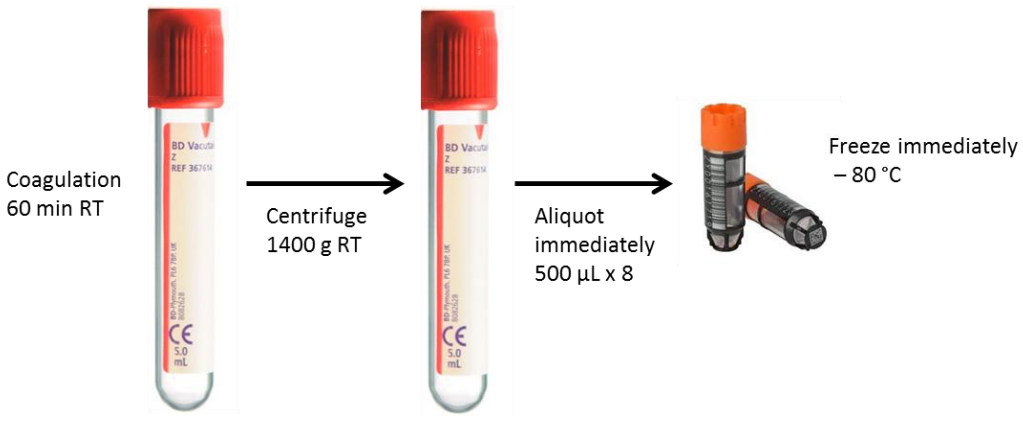
It is important to let the blood coagulate in an upright position at RT for 60 minutes. Centrifuge the sample and immediately aliquot and freeze the aliquots within 90 minutes after sample collection. Register the samples according to the local protocol and log all deviations on the same registration form.

Material and instrumentation:

- 3 x 5 ml BD VACUTAINER serum glass tube with no additive (367614)
- 8 x 0.7 ml FluidX (68-0702-11)
- Centrifuge for vacutainer tubes
- Barcode reader
- -80°C freezer

Collection, preparation and storage:

7. Collect whole blood into BD VACUTAINER glass tubes containing no additive.
8. Incubate in an upright position at room temperature for 60 min (no longer than 60 min) to allow clotting.
9. Centrifuge for 12 min at 1400 x g at room temperature.
10. Inspect serum for turbidity. Turbid samples should be centrifuged again to remove remaining insoluble matter. A new centrifugation must be indicated as a deviation.
11. Aliquot 500 µL serum into 8 x 0.7 ml FluidX tubes.
12. Freeze the aliquots at -80°C within 90 min after sample collection.
13. Use the barcode reader for registration of the sample. Register the samples according to the local protocol and log all deviation on the same registration form.
14. Sample aliquots are stored at -80C and shipped on dry ice in the original FluidX boxes (x 48 tubes).
15. Samples must **never** be allowed to warm or thaw except from when to be used in analyses. Any deviation from this must be **registered**. Number and date of thawing an aliquot for analyses must be registered.



Responsible:
Contact person for biosampling and laboratory preparation: Siri Hinteregger, MBF
Contact person for Biobank: Hilde Kristin Garberg

4.5 Platelet isolation and cryopreservation for mitochondrial research

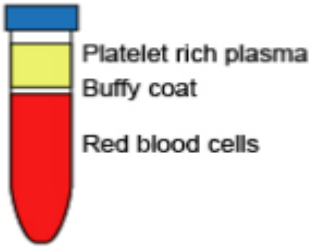
Performed at: Bergen

Material and instrumentation

Item	How many	Supplier	Cat no	Comment
VACUETTE® TUBE 9 ml ACD-A	1	Greiner Bio-One	456055	
10 ml Falcon centrifugation tubes				
DMSO				
Pipettes & tips				
-80°C freezer		Study center		

Collection, preparation and storage:

1. Collect whole blood in vacutainer ACD tubes (yellow cap) 9ml?
2. Mix gently by slowly inverting the tube
3. Spin at room temperature at 200g for 20min, no brake
4. After the spin, three distinct layers can be observed:
    a. the top: straw-colored layer contains platelets
5. Transfer about two thirds of the **top layer** into a new 10ml Falcon tube
6. Freeze the cells in their own plasma adding DMSO at a final concentration of 5-6%
7. Store at -80°C



Responsible:

Contact person for biosampling and laboratory preparation: Siri Hinteregger, MBF
Contact person for Biobank: Hilde Kristin Garberg

4.6 Collection, of cerebrospinal fluid

Material and instrumentation:

Item	How many	Supplier	Cat no	Comment
Standard lumbar puncture equipment				
Standard CSF cell count tubes	2			
5 ml PolyPropylene (PP) cryo-s tube with red PP cap	2	Greiner Bio-One via VWR	479-4154	2 uker
0.7 ml FluidX tubes (PP)	15	Pedro Consulting	68-0702-11N	
5 ml PP tube for dementia biomarkers	1	Sarstedt	63-504-027	
Barcode reader				
Centrifuge for centrifugation tubes		Study center		

PP PIPETTE TIPS (ART 1000µL REACH)		VWR	732-2215 (2079-HR)	Alternative tip will be used
Pipettes		Study center		
-80°C freezer		Study center		

4.6.1 Collection of cerebrospinal fluid

Absolute contraindications for the procedure:

- Thrombocytes less than 40 x 10^9/L
- Use of anticoagulation (except ASA)
- INR >1.7 (warfarin users)
- Local infection at the biopsy site
- Any other center-specific clinical routines and/or guidelines MUST be followed

During lumbar punction the following procedures should take place:

1. If noticeably bloody tap, discard the first 1-2 ml until CSF is clear
2. 10 drops spinal fluid collected in standard tube for cell count (erythrocytes and leucocytes)
3. 5 ml x 2 is collected in 5 ml sterile PolyPropylene tubes (479-4154) for biobanking (see materials and preparation below)
4. 2 ml is collected in 5 ml PP tube for dementia biomarkers (63-504-027) for clinical analysis of abeta42, t-tau and p-tau181.
5. 10 drops spinal fluid collected in standard tube for cell count (erythrocytes and leucocytes)

NB! Do not use pressure measurements tubing – collect CSF DIRECTLY into the tubes

NB! Only polypropylene (PP) pipette tips should be used to collect and handle the CSF!

4.6.2 Processing and storage of cerebrospinal fluid

1. **The collected 5ml x 2 CSF in "5 ml PolyPropylene (PP) cryo-s tube with red PP cap"**
   a. **NB! The sample has to be centrifuged within 30 min from collection!**
   b. Centrifuge within 30 min at 2,000 g, at 4 °C, for 10 min
   c. Transfer the supernatant to 2 x new "5 ml PolyPropylene (PP) cryo-s tube with red PP cap" – use PP pipette tips
   d. Mix carefully by inverting the tube x 7-10 times (or mild vortexing)
   e. Aliquot 500 µl CSF per tube into 0.7 ml FluidX tubes - use PP pipette tips
   f. Freeze the aliquots at -80°C.
   g. Sample aliquots are stored at -80C and shipped on dry ice in the original FluidX boxes (x 48 tubes).
   h. Samples must **never** be allowed to warm or thaw except from when to be used in analyses. Any deviation from this must be **registered**. Number and date of thawing an aliquot for analyses must be registered.

2. **The collected 2 ml CSF in 5 ml PP tube for dementia biomarkers will be used for analysis of abeta42, t-tau and p-tau181:**
   a. Transfer to -80C immediately after collection.
   b. Samples are stored at -80C in freezer-compatible cardboard or plastic storage boxes.
   c. Samples are shipped on dry ice.
   d. Further handling:

   i. Bergen will send batches of 20 samples to Akershus University Hospital for dementia marker analysis
   ii. Trondheim will send batches of 20 samples to Akershus University Hospital for dementia marker analysis
   iii. London will send this along with the rest of the CSF sample to Bergen (see below).

3. Samples must **never** be allowed to warm or thaw except from when to be used in analyses. Any deviation from this must be **registered**. The number and date of thawing an aliquot for analyses must be registered.

Responsible:

Contact person for biosampling and laboratory preparation: Siri Hinteregger, MBF
Contact person for Biobank: Hilde Kristin Garberg

4.7 Fecal sample for biobanking

Performed at: HUS

Fecal samples from the last 24h will be collected according to standard clinical routines and stored at -80C. The patient must bring a 3-day diet registration from together with the fecal sample om the morning of each visit. For details on fecal sample collection and storage, see document: “SOP for fecal sample collection” (Prosedyre for avføringsprøvetaking hjemme).

Responsible:
Bergen: Birgitte Betrentsen

4.8 Urine for biobanking

Performed at: HUS

Morning urine will be collected according to standard clinical routines, aliquoted and stored at -80C.

Responsible:

Bergen: Hanne Linda Nakkestad

5 CONTACT PERSONS

The following chapter summarizes the contact persons and responsible investigators for the sub-studies:

5.1 Helse Bergen

5.1.1 Biobank Haukeland

Contact persons regarding biobanking, sample shipment, sample registration

Ann Cathrine Kroksveen	55971970 / 92031413, ann.cathrine.kroksveen@helse-bergen.no
Hilde Garberg	55975854 / 55973149, hilde.kristin.garberg@helse-bergen.no

5.1.2 Laboratory Clinic

Contact person regarding safety laboratory, serology and hormone analyses

Siri Hinteregger	55973124, siri.hinteregger@helse-bergen.no

5.1.3 Department of Neurology

Contact person for cells, CSF collection

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APPENDIX B - MRI AND FDG-PET – PROTOCOL, N-DOSE

Revised May 2025

Contact persons:

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- Njål Brekke (njal.brekke@helse-bergen.no)
- Vivian Skjeie (vivian.skjeie@helse-bergen.no)
- Cecilie Brekke Rygh (cecilie.brekke.rygh@helse-bergen.no)

Bergen:

Equipment:

Scanner: Siemens Biograph mMR 3T (PET/MR)

Software: E11P

Coils: RAPID Biomedical 31P – H_Head Coil 3T Human head V-XQ-HQ-030-01921 V01 for SIEMENS Biograph mMR 3T

To PACS: Clinical protocol

To fPACS: All sequences (entire examination)

Protocol:

Participant preparation:

The participant should fast a minimum of 6 hours before injection of 18F-FDG. A peripheral venous catheter (PVC) is then placed in the medial cubital vein. Blood glucose is measured. The required blood glucose level is below 8 mmol/L. 30 minutes before the scan 250 MBq of 18F-FDG is injected into the PVC. The participant is required to lie in a quiet, dark environment during the interval after injection and before scanning to minimize brain activity. The participants should not use mobile phones or headphones during this period. Eyes must be closed for fMRI sequences. Imaging is to be taken up to 72 hours before or after physical examination of participants.

Positioning: Localizer. Auto align if possible.

Scan parameters: Scan labelled by study ID.

MRI sequences:

- Localizer for planning of MR and PET – 1.0 min.
- 3D T1 (sagittal, 1x1x1 mm, 3D-BRAVO or MPRAGE) – 5.5 min.
- Attenuation correction map, generated using DeepMRAC[1] – 2.0 min.
- 31P-MRS calibration: FID, multinuclear coil, generated using xnuccalc2 from NMproc-Dockers – 2 min.
-
- 31P-MRS sequence: CSI, multinuclear coil – 15 min.

Total imaging time: 25.5 min imaging time - 35 min including changing the coil for CSI.

Specific procedures for 31P-MRS image analysis:

Spectra from the occipital region will be aligned using an adaption of the Spectral Registration implementation from Gannet 3.022[2,3], subject to thresholding on SNR (>=3) to eliminate the majority of out-of-brain voxels.

Voxels will then be averaged before being processed in Matlab 9.5 (the MathWorks, Natick, MA) using the OXSA toolbox[4] utilizing first order phase correction and fitting with AMARES.

Custom prior information was created based on literature values for membrane phospholipids (MP), glycerophosphocholine (GPC), glycerophosphoethanolamine (GPE), inorganic phosphate (Pi), phosphocoline (PC), phosphoethanolamine (PE) as well as alpha-, beta- and gamma resonances of adenosine triphosphate (ATP-α, -β, and –γ, respectively) in reference to the phosphocreatine (PCr) peak[5–7].

Additional information for the properties of nicotinamide adenine dinucleotide (NAD) was added based on the framework developed by Lu and colleagues[8] by calculating field-strength dependent chemical shift differences, relative amplitudes and frequency separations for oxidized and reduced NAD (NAD^+ and NADH, respectively).

Linewidths will be fixed to be equal for NAD^+, NADH and ATP-α. At 3T, and to comply with normal-mode specific absorption rate (SAR) restrictions, peak separation for NAD^+ and NADH is likely to be limited and therefore only combined values of total NAD (NAD^+ and NADH together) will most likely be reported.

Fitted peak amplitudes and areas are used to calculate total NAD in proportion to a normalisation constant such as ATP-α or PCr. This normalised NAD-value will be used for the planned statistical analysis defined in the trial SAP.

Specific procedures for NRRP and PDRP image analysis of FDG-PET images

FDG-PET scans will be transferred electronically to the Center for Neurosciences at The Feinstein Institutes for Medical Research (Manhasset, NY, USA) and analyzed using automated computing pipelines implemented in MATLAB R2023b (MathWorks, Natick, MA). Images will first be pre-processed using Statistical Parametric Mapping (SPM12) software (http://fil.ion.ucl.ac.uk/spm; Wellcome Centre for Human Neuroimaging, London, UK). FDG-PET scans acquired at visits V1, V 2, V3 and V4 will be aligned to produce a mean image, which will be spatially normalized in standard Montreal Neurological Institute (MNI) anatomic space along with the individual scans from each time point. The normalized images will then be smoothed with a 10-mm Gaussian filter in three dimensions to enhance the signal to noise ratio.

In the previous NADPARK phase-I study[9], we identified a specific NR-related metabolic pattern (NRRP) from paired metabolic scan data from participants in the NR 1000 mg group analyzed using ordinal trends/canonical variates analysis (OrT/CVA)—a supervised form of principal component analysis (PCA)[10]. This multivariate approach was designed to detect and quantify regional covariance patterns (i.e., metabolic networks) for which expression values (i.e., subject scores) increase or decrease with treatment in all or most of the subjects[11–15]. The significance of the resulting OrT/CVA topographies, i.e., the NRRP[9], was assessed using nonparametric tests, i.e., permutation testing of the subject scores to show that the observed ordinal trend does not occur by chance. Likewise, the reliability of the voxel loadings (i.e., region weights) on the resulting NRRP network topography was assessed using bootstrap resampling procedures[12,16].

For this study protocol, pre-processed FDG-PET scans of individual subjects will be used to compute the expression values (subject scores) of NRRP at baseline and the follow-up timepoints, using the GCVA PCA software (available at https://www.nitrc.org/projects/gcva_pca) for Ordinal Trend

(OrT/CVA) Analysis[10]. NRRP subject scores will be standardized (*z*-scored) to computed expression values for this pattern in an age-matched group of healthy volunteers scanned at the Feinstein Institutes.

FDG-PET scans will also be used to compute the expression values of the PD-related metabolic pattern (termed PDRP)[17] which was identified and validated previously in several independent patient populations. Subject scores for PDRP and ADRP of individual subjects will be computed automatically on a single-scan basis at each study visit and in a blinded fashion, using in-house Scan Analysis and Visualization (ScAnVP) software (available at http://feinsteinneuroscience.org). The subject scores of each pattern will be standardized (*z*-scored) in reference to corresponding scores of age-matched healthy controls.

Outcome measures of the NRRP and PDRP z-scores for individual subjects at each study visit will be reported in tabular format and transferred electronically to the Norway group for the planned statistical analysis defined in the trial SAP.

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APPENDIX C - CLINICAL RATING SCALES

1 GENERAL INFORMATION

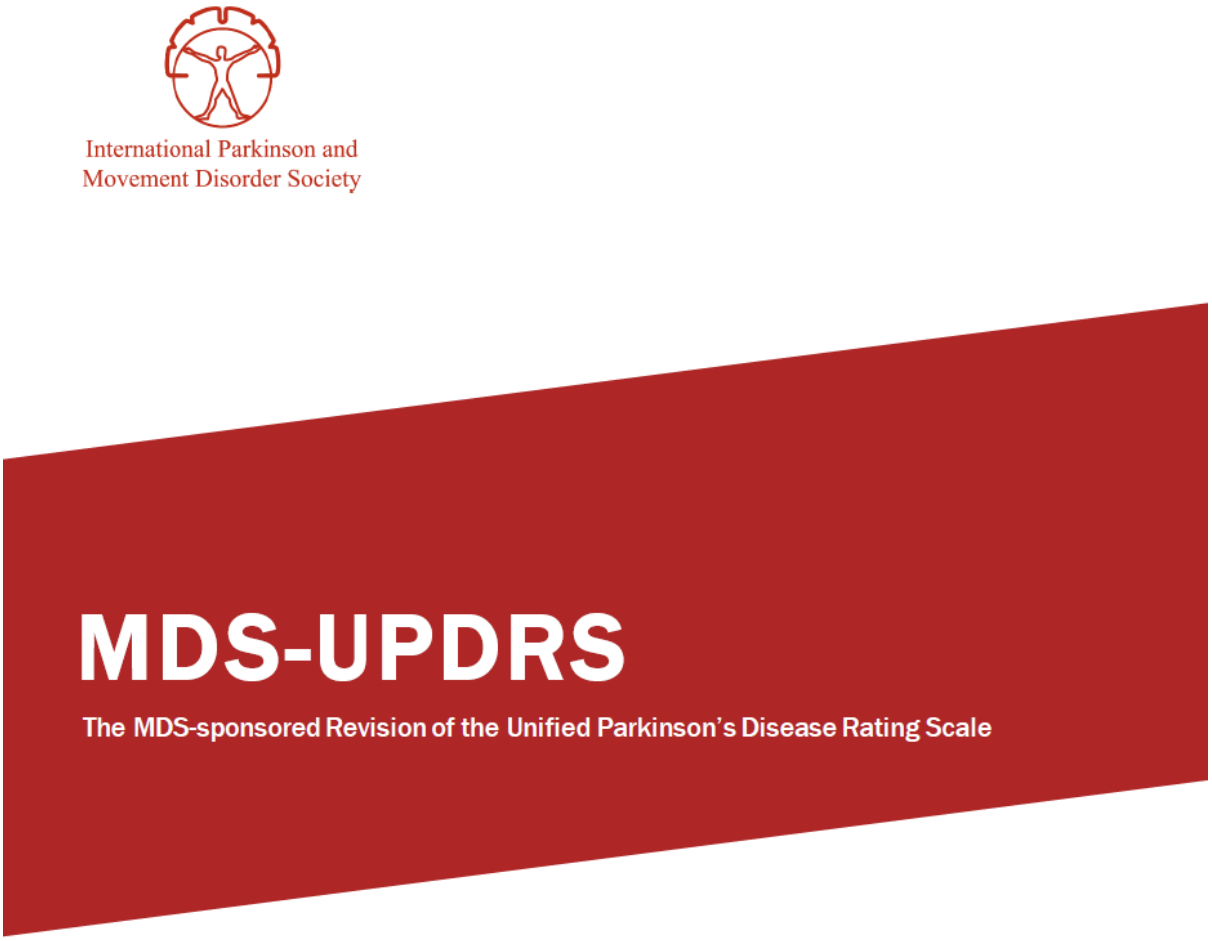
The following appendix lists the clinical rating scales used in the N-DOSE study. Where clinical rating scales were used in specific sequences, this has been specified.

2 MRS-UPDRS

The MDS-Sponsored Revision of the Unified Parkinson's Disease Rating Scale

For Part 1, part 3 and part 4, the English version was used. For part 2, the Norwegian version of the questionnaire was used.

MRS-UPDRS – Page 1



MRS-UPDRS – Page 2

MDS Permissions

The MDS-sponsored revision of the UPDRS (MDS-UPDRS) is owned and licensed by the International Parkinson and Movement Disorder Society (MDS). Permission is required to use the scale and can be obtained by submitting a Permissions Request Form on the MDS website. For licensing inquiries, please e-mail info@movementdisorders.org.

Unauthorized reproduction, distribution, translation, or sale of any portion of the MDS-UPDRS is strictly prohibited. Changes, modifications and derivative works of the scale are not permitted without the express authorization of MDS. Including but not limited to the following, the MDS-UPDRS may not be incorporated into clinical trials, training materials, certification programs, software programs, electronic platforms, electronic medical records, databases, or devices except by permission of MDS.

MRS-UPDRS – Page 3

MDS-UPDRS

The Movement Disorder Society (MDS)-sponsored new version of the UPDRS is founded on the critique that was formulated by the Task Force for Rating Scales in Parkinson's Disease (*Mov Disord* 2003;18:738-750). Thereafter, the MDS recruited a Chairperson to organize a program to provide the Movement Disorder community with a new version of the UPDRS that would maintain the overall format of the original UPDRS, but address issues identified in the critique as weaknesses and ambiguities. The Chairperson identified subcommittees with chairs and members. Each part was written by the appropriate subcommittee members and then reviewed and ratified by the entire group. These members are listed below.

The MDS-UPDRS has four parts: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living), Part III (motor examination) and Part IV (motor complications). Part I has two components: IA concerns a number of behaviors that are assessed by the investigator with all pertinent information from patients and caregivers, and IB is completed by the patient with or without the aid of the caregiver, but independently of the investigator. These sections can, however, be reviewed by the rater to ensure that all questions are answered clearly and the rater can help explain any perceived ambiguities. Part II is designed to be a self-administered questionnaire like Part IB, but can be reviewed by the investigator to ensure completeness and clarity. Of note, the official versions of Part IA, Part IB and Part II of the MDS-UPDRS do not have separate "ON" or "OFF" ratings. However, for individual programs or protocols the same questions can be used separately for "ON" and "OFF". Part III has instructions for the rater to give or demonstrate to the patient; it is completed by the rater. Part IV has instructions for the rater and also instructions to be read to the patient. This part integrates patient-derived information with the rater's clinical observations and judgments and is completed by the rater.

The authors of this new version are:

Chairperson: Christopher G. Goetz
Part I: Werner Poewe (chair), Bruno Dubois, Anette Schrag
Part II: Matthew B. Stern (chair), Anthony E. Lang, Peter A. LeWitt
Part III: Stanley Fahn (chair), Joseph Jankovic, C. Warren Olanow
Part IV: Pablo Martinez-Martin (chair), Andrew Lees, Olivier Rascol, Bob van Hilten
Development Standards: Glenn T. Stebbins (chair), Robert Holloway, David Nyenhuis
Appendices: Cristina Sampaio (chair), Richard Dodel, Jaime Kulisevsky
Statistical Testing: Barbara Tilley (chair), Sue Leurgans, Jean Teresi
Consultant: Stephanie Shaftman, Nancy LaPelle

Contact:
International Parkinson and Movement Disorder Society
555 East Wells Street, Suite 1100
Milwaukee, WI USA 53202

Telephone: 414-276-2145
Email: info@movementdisorders.org

July 1, 2008

MRS-UPDRS – Page 4

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 IA is administered by the rater (six questions) and focuses on complex behaviors. Part IB is a component of the self-administered Patient Questionnaire that covers seven questions on non-motor experiences of daily living.

Part IA:
In administering Part IA, the examiner should use the following guidelines:

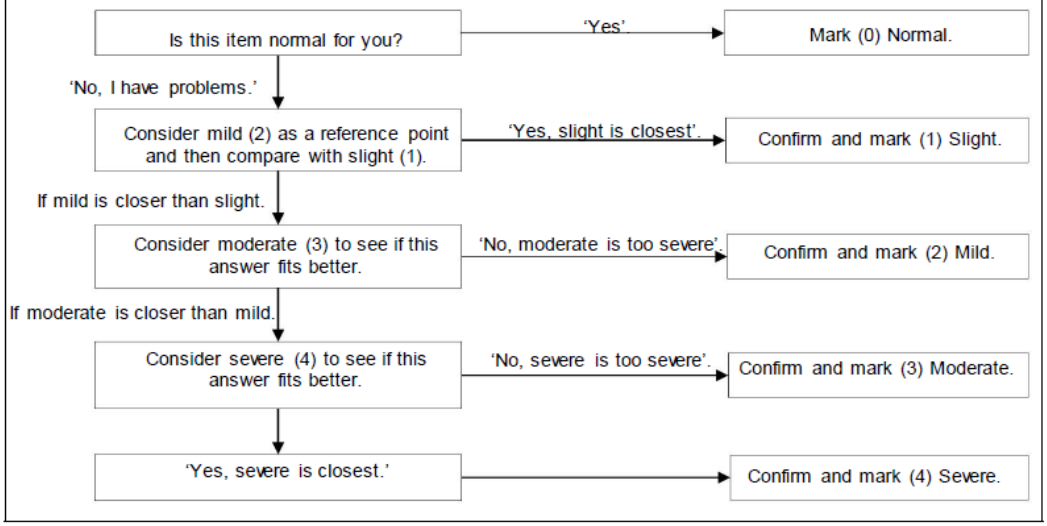
1. Mark at the top of the form the primary data source as patient, caregiver, or patient and caregiver in equal proportion.
2. The response to each item should refer to a period encompassing the prior week including the day on which the information is collected.
3. All items must have an integer rating (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 IA

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.



MRS-UPDRS – Page 5

Patient Name or Subject ID	Site ID	_____ - _____ - _____ (mm-dd-yyyy) Assessment Date	Investigator's Initials

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

Part IA: Complex behaviors: [completed by rater]

Primary source of information:

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

To be read to the patient: I am going to ask you six questions about behaviors that you may or may not experience. Some questions concern common problems and some concern uncommon ones. If you have a problem in one of the areas, please choose the best response that describes how you have felt MOST OF THE TIME during the PAST WEEK. If you are not bothered by a problem, you can simply respond NO. I am trying to be thorough, so I may ask questions that have nothing to do with you.

1.1 COGNITIVE IMPAIRMENT	SCORE
Instructions to examiner: Consider all types of altered level of cognitive function including cognitive slowing, impaired reasoning, memory loss, deficits in attention and orientation. Rate their impact on activities of daily living as perceived by the patient and/or caregiver. *Instructions to patient [and caregiver]: Over the past week have you had problems remembering things, following conversations, paying attention, thinking clearly, or finding your way around the house or in town?* [If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No cognitive impairment. 1: Slight: Impairment appreciated by patient or caregiver with no concrete interference with the patient's ability to carry out normal activities and social interactions. 2: Mild: Clinically evident cognitive dysfunction, but only minimal interference with the patient's ability to carry out normal activities and social interactions. 3: Moderate: Cognitive deficits interfere with but do not preclude the patient's ability to carry out normal activities and social interactions. 4: Severe: Cognitive dysfunction precludes the patient's ability to carry out normal activities and social interactions.	☐

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	SCORE
1.2 HALLUCINATIONS AND PSYCHOSIS Instructions to examiner: 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 patient's insight into hallucinations and identify delusions and psychotic thinking. *Instructions to patient [and caregiver]: 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.] 0: Normal: No hallucinations or psychotic behavior. 1: Slight: Illusions or non-formed hallucinations, but patient recognizes them without loss of insight. 2: Mild: Formed hallucinations independent of environmental stimuli. No loss of insight. 3: Moderate: Formed hallucinations with loss of insight. 4: Severe: Patient has delusions or paranoia.	☐
1.3 DEPRESSED MOOD Instructions to examiner: 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. *Instructions to patient [and caregiver]: 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.] 0: Normal: No depressed mood. 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. 2: Mild: Depressed mood that is sustained over days, but without interference with normal activities and social interactions. 3: Moderate: Depressed mood that interferes with, but does not preclude the patient's ability to carry out normal activities and social interactions. 4: Severe: Depressed mood precludes patient's ability to carry out normal activities and social interactions.	☐

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	SCORE
1.4 ANXIOUS MOOD Instructions to examiner: 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. *Instructions to patient [and caregiver]: 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.] 0: Normal: No anxious feelings. 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. 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. 3: Moderate: Anxious feelings interfere with, but do not preclude, the patient's ability to carry out normal activities and social interactions. 4: Severe: Anxious feelings preclude patient's ability to carry out normal activities and social interactions.	☐
1.5 APATHY Instructions to examiner: 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. *Instructions to patient [and caregiver]: 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.] 0: Normal: No apathy. 1: Slight: Apathy appreciated by patient and/or caregiver, but no interference with daily activities and social interactions. 2: Mild: Apathy interferes with isolated activities and social interactions. 3: Moderate: Apathy interferes with most activities and social interactions. 4: Severe: Passive and withdrawn, complete loss of initiative.	☐

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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/her 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 patient [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 patient.]	
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].

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Spørreskjema for pasienter

Instruksjoner:

Dette spørreskjemaet tar for seg erfaringer i dagliglivet.
Det er 20 spørsmål. Vi prøver å være grundige, og noen av disse spørsmålene er kanskje ikke aktuelle for deg nå eller noen gang. Hvis du ikke har problemer, bare svar 0 for NEI.
Vennligst les hvert spørsmål nøye og les alle svarene før du velger det som passer best for deg.

Vi er interessert i ditt gjennomsnittlige eller vanlige funksjonsnivå i løpet av den siste uken inkludert i dag. Noen pasienter kan gjøre ting bedre på en tid av dagen enn på andre tider. Men bare ett svar er tillatt for hvert spørsmål, så vennligst marker det svaret som best beskriver hva du kan gjøre mesteparten av tiden.

Du har kanskje andre sykdommer i tillegg til Parkinsons sykdom. Ikke prøv å skille Parkinsons fra andre sykdommer. Bare svar på spørsmålet så godt du kan.

Bruk bare 0, 1, 2, 3, 4 i svarene, ikke noe annet. Ikke la noen svar stå åpne.

Legen eller sykepleieren kan gå igjennom spørsmålene med deg, men det er meningen at pasienter skal fylle ut spørreskjemaet, enten alene eller sammen med en omsorgsperson.

Hvem fyller ut dette spørreskjemaet? (svar det som passer best)

Pasient ☐

Omsorgsperson ☐

Pasient og omsorgsperson i like stor grad ☐

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Del 1: Ikke-motoriske aspekter ved erfaringer i dagliglivet (iM-EDL)

1.7 SØVNVANSKER

I løpt av den sist uken, har du hatt problemer med å sovne om kvelden eller forblittt våken gjennom natten? Tenk over hvor uthvilt du følte deg etter å ha våknet om morgenen.

0: Normal:	Ingen problemer.
1: Meget lett:	Søvnvansker er tilstede, men gir vanligvis ikke problemer med å få en full natts søvn.
2: Mild:	Søvnvansker gir noen problemer med å få en full natts søvn.
3: Moderat:	Søvnvansker gir mye problemer med å få en full natts søvn, men jeg sover vanligvis mer enn halve natten.
4: Alvorlig:	Vanligvis sover jeg ikke mesteparten av natten.

1.8 SØVNIGHET PÅ DAGTID

I løpet av den siste uken, har du hatt problemer med å holde deg våken på dagtid?

0: Normal:	Ingen søvnighet på dagtid.
1: Meget lett:	Søvnighet på dagtid forekommer, men jeg kan stå imot og holder meg våken.
2: Mild:	Noen ganger sovner jeg når jeg er alene og slapper av, for eksempel når jeg leser eller ser TV.
3: Moderat:	Av og til sovner jeg når jeg ikke burde, for eksempel når jeg spiser eller snakker med andre mennesker.
4: Alvorlig:	Jeg sovner ofte når jeg ikke burde, for eksempel når jeg spiser eller snakker med andre mennesker.

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1.9 SMERTE OG ANDRE SANSEOPPLEVELSER

I løpet av den siste uken, har du hatt ubehagelige følelser i kroppen som smerter, verking, prikkinger eller kramper?

0: Normal:	Ingen ubehagelige følelser.
1: Meget lett:	Jeg har slike følelser, men jeg kan gjøre ting og være sammen med andre mennesker uten vanskeligheter.
2: Mild:	Disse følelsene gir meg noen problemer når jeg gjør ting eller er sammen med andre mennesker.
3: Moderat:	Disse følelsene gir meg mye problemer, men de hindrer meg ikke fra å gjøre ting eller være sammen med andre mennesker.
4. Alvorlig:	Disse følelsene hindrer meg i å gjøre ting eller være sammen med andre mennesker

1.10 VANNLATINGSPROBLEMER

I løpet av den siste uken, har du hatt problemer med kontroll over vannlatingen? For eksempel et plutselig behov for å late vannet, en trang til å late vannet for hyppig, eller uhell med vannlatingen?

0: Normal:	Ingen problemer med kontrollen over vannlatingen.
1: Meget lett:	Jeg må late vannet ofte eller med en gang jeg kjenner trang. Men disse problemene gir meg ingen vanskeligheter i mine daglige aktiviteter.
2: Mild:	Vannlatingsproblemer gir meg noe problemer i daglige aktiviteter, men jeg har ikke hatt uhell med vannlatingen.
3: Moderat:	Vannlatingsproblemer gir meg mye problemer i daglige aktiviteter, inkludert uhell med vannlatingen.
4: Alvorlig:	Jeg kan ikke kontrollere vannlatingen og bruker truseinnlegg eller har blærekateter.

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1.11 PROBLEMER MED FORSTOPPELSE

Har du i løpet av den siste uken hatt problemer md forstoppelse som medfører at du har vanskeligheter med å få avføring?

0: Normal:	Ingen forstoppelse.
1: Meget lett:	Jeg har hatt forstoppelse, jeg bruker ekstra krefter på å ha avføring. Dette forstyrrer imidlertid ikke mine daglige aktiviteter eller velvære.
2: Mild:	Forstoppelse medfører problemer i aktiviteter eller velvære.
3: Moderat:	Forstoppelse medfører mye problemer i aktiviteter eller velvære. Det hindrer meg imidlertid ikke i aktiviteter.
4: Alvorlig:	Jeg trenger vanligvis fysisk hjelp av noen for å tømme tarmen.

1.12 SVIMMELHET I STÅENDE STILLING

Har du i løpet av den siste uken følt deg svimmel, tåkete eller at du vil besvime når du reiser deg opp fra sittende eller liggende stiling?

0: Normal:	Ingen svimmelhet eller tåkefølelse.
1: Meget lett:	Svimmelhet eller tåkefølelse forekommer. Det hindrer meg imidlertid ikke i å gjøre noe.
2: Mild:	Svimmelhet eller tåkefølelse medfører at jeg må holde meg fast, men jeg trenger ikke å sette meg eller legge meg ned.
3: Moderat:	Svimmelheteller tåkefølelse medfører at jeg må sette meg eller legge meg ned for å unngå å besvime eller falle.
4: Alvorlig:	Svimmelhet eller tåkefølelse fører til at jeg faller eller besvimer.

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1.13 UTMATTETHET

Har du stort sett følt deg utmattet den siste uken? Denne følelsen er ikke ledd i å være trett eller trist.

0: Normal:	Ingen utmattethet.
1: Meget lett:	Utmattethet forekommer. Det medfører imidlertid ikke problemer med å gjøre ting eller være sammen med mennesker.
2: Mild:	Utmattethet medfører noen problemer med å gjøre ting eller være sammen med mennesker.
3: Moderat:	Utmattethet medfører mye problemer med å gjøre ting eller være sammen med mennesker. Det stopper meg imidlertid ikke fra å gjøre noe.
4: Alvorlig:	Utmattethet hindrer meg i å gjøre ting eller være sammen med mennesker.

Del II: Motoriske aspekter ved erfaringer i dagliglivet (M-EDL)

2.1 TALE

I løpet av den siste uken, har du hatt problemer med talen?

0: Normal:	Ikke i det hele tatt (Ingen problemer).
1: Meget lett:	Talen min er svak, skurret og ujevn, men det medfører ikke at andre ber meg gjenta meg.
2: Mild:	Talen min medfører at andre av og til ber meg gjenta, men ikke hver dag.
3: Moderat:	Talen min er så utydelig at andre ber meg gjenta hver dag selv om mesteparten av talen min blir forstått.
4: Alvorlig:	Mesteparten eller all tale er uforståelig.

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2.2 SPYTT OG SIKLING

I løpet av den siste uken, har du vanligvis hatt for mye spytt mens du er våken eller mens du sover?

0: Normal:	Ikke i det hele tatt (ingen problemer).
1: Meget lett:	Jeg har for mye spytt, men sikler ikke.
2: Mild:	Jeg sikler noe mens jeg sover, men ikke når jeg er våken.
3: Moderat:	Jeg sikler noe når jeg er våken, men jeg trenger vanligvis ikke tørkepapir eller lommetørkle.
4: Alvorlig:	Jeg sikler så mye at jeg regelmessig trenger tørkepapir eller lommetørkle for å beskytte klærne mine.

2.3 TYGGING OG SVELGING

I løpet av den siste uken, har du vanligvis problemer med å svelge tabletter eller spise måltider? Må tablettene være delt eller knust eller maten bløt, kuttet opp eller most for at du skal unngå å svelge vrangt?

0: Normal:	Ingen problemer.
1: Meget lett:	Jeg vet jeg tygger sakte og bruker ekstra krefter på å svelge, men jeg svelger ikke vrangt eller behøver maten min spesielt tilberedt.
2: Mild:	Jeg må ha tablettene delt eller maten spesielt tilberedt på grunn av problemer med tygging eller svelging, men jeg har ikke svelget vrangt i løpet av den siste uken.
3: Moderat:	Jeg har svelget vrangt minst en gang i løpet av den siste uken.
4: Alvorlig:	Jeg trenger ernæringssonde på grunn av problemer med tygging og svelging.

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2.4 SPISING

I løpet av den siste uken, har du vanligvis hatt problemer md å håndtere mat og bruke spisebestikk? Har du for eksempel problemer med å håndtere fingermat eller bruke gafler, kniver, skjeer, spisepinner?

0: Normal:	Ingen problemer
1: Meget lett:	Jeg er langsom, men trenger ikke hjelp og søler ikke mens jeg spiser.
2: Mild:	Jeg er langsom når jeg spiser og søler mat av og til. Jeg kan trenge hjelp med noen oppgaver slik som å skjære opp kjøtt.
3: Moderat:	Jeg trenger hjelp med mange spiseoppgaver men kan klare noen alene.
4: Alvorlig:	Jeg trenger hjelp til de fleste eller alle spiseoppgaver.

2.5 PÅKLEDNING

I løpet av den siste uken, har du hatt problemer med å kle på deg? Er du for eksempel langsom eller trenger hjelp med å kneppe knapper, bruke glidelåser, ta på eller av klær eller smykker?

0: Normal:	Ikke i det hele tatt (ingen problemer).
1: Meget lett:	Jeg er langsom, men trenger ikke hjelp.
2: Mild:	Jeg er langsom og trenger hjelp til noen få oppgaver (knapper, armbånd)
3. Moderat:	Jeg trenger hjelp til mange påkledningsoppgaver.
4: Alvorlig:	Jeg trenger hjelp til de fleste eller alle påkledningsoppgaver.

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2.6 HYGIENE

I løpet av den siste uken, har du vanligvis vært langsom eller trenger du hjelp med å vaske deg, bade, barbere deg, pusse tenner, gre håret eller med annen personlig hygiene?

0: Normal:	Ikke i det hele tatt (ingen problemer).
1: Meget lett;	Jeg er langsom, men jeg trenger ikke hjelp.
2: Mild:	Jeg trenger noen til å hjelpe meg med enkelte hygieneoppgaver.
3. Moderat:	Jeg trenger hjelp til mange hygieneoppgaver.
4: Alvorlig:	Jeg trenger hjelp til de fleste eller alle hygieneoppgaver.

2.7 HÅNDSKRIFT

I løpet av den siste uken, har andre vanligvis hatt problemer med å lese håndskriften din?

0: Normal:	Ikke i det hele tatt (ingen problemer).
1: Meget lett:	Jeg skriver langsomt, klønete eller ujevnt, men alle ord er tydelige.
2: Mild:	Noen ord er utydelige og vanskelige å lese.
3: Moderat:	Mange ord er utydelige og vanskelige å lese.
4: Alvorlig:	De fleste eller alle ordene er uleselige.

2.8 HOBBYER OG ANDRE AKTIVITETER

I løpet av den siste uken, har du vanligvis hatt problemer med å utøve hobbyer eller andre ting du liker å gjøre?

0: Normal:	Ikke i det hele tatt (ingen problemer).
1: Meget lett:	Jeg er litt langsom, men utfører disse aktivitetene lett.
2: Mild:	Jeg har noen vanskeligheter med å utføre disse aktivitetene.
3: Moderat:	Jeg har store problemer med å utføre disse aktivitetene, men gjør likevel de fleste.
4: Alvorlig:	Jeg er ikke i stand til å utføre de fleste eller alle disse aktivitetene

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2.9 SNU SEG I SENGEN
I løpet av den siste uken, har du vanligvis hatt problemer med å snu deg i sengen?

0: Normal:	Ikke i det hele tatt (Ingen problemer)
1: Meget lett:	Jeg har noen problemer med å snu meg, men jeg trenger ikke hjelp.
2: Mild:	Jeg har mye problemer med å snu meg, og trenger av og til hjelp fra noen andre.
3: Moderat:	Jeg trenger ofte hjelp fra noen andre for å snu meg.
4: Alvorlig:	Jeg kan ikke snu meg uten hjelp fra andre.

2.10 SKJELVING
I løpet av den siste uken, har du hatt regelmessig skjelving eller risting?

0: Normal:	Ikke i det hele tatt, jeg har ikke skjelvinger eller ristinger.
1: Meget lett:	Ristinger eller skjelvinger forekommer, men forårsaker ikke problemer i noen aktiviteter.
2: Mild:	Ristinger og skjelvinger forårsaker problemer bare i noen få aktiviteter.
3: Moderat:	Ristinger og skjelvinger forårsaker problemer i mange av mine daglige aktiviteter.
4: Alvorlig:	Ristinger eller skjelvinger forårsaker problemer i de fleste eller alle aktiviteter.

2.11 KOMME SEG UT AV SENGEN, EN BIL ELLER EN DYP STOL
I løpet av den siste uken, har du vanligvis hatt problemer med å komme deg ut av sengen, et bilsete eller en dyp stol?

0: Normal:	Ikke i det hele tatt (ingen problemer).
1: Meget lett:	Jeg er langsom eller klossete, men klarer det vanligvis på første forsøk.
2: Mild:	Jeg trenger mer enn ett forsøk eller trenger hjelp av og til.
3: Moderat:	Jeg trenger noen ganger hjelp for å komme opp, men for det meste klarer jeg det fortsatt selv.
4: Alvorlig:	Jeg trenger hjelp mesteparten eller hele tiden.

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2.12 GANGE OG BALANSE

I løpet av den siste uken, har du vanligvis hatt problemer med balanse og gange?

0: Normal:	Ikke i det hele tatt (ingen problemer)
1. Meget lett:	Jeg er litt langsom eller kan dra på et ben. Jeg bruker aldri ganghjelpemidler.
2: Mild:	Jeg bruker av og til et ganghjelpemiddel, men jeg trenger ikke hjelp fra en annen person.
3: Moderat:	Jeg bruker vanligvis et ganghjelpemiddel (stokk, rullator) for å gå trygt uten å falle. Men jeg trenger vanligvis ikke støtte fra en annen person.
4: Alvorlig:	Jeg bruker vanligvis støtte av en annen person for å gå trygt uten å falle.

2.13 TILSTIVNING

I løpet av den siste uken, på en vanlig dag mens du går, stopper du plutselig eller stivner til som om føttene dine henger fast i gulvet?

0: Normal:	Ikke i det hele tatt (Ingen problemer).
1: Meget lett:	Jeg stivner til kortvarig, men kan lett starte å gå igjen. Jeg trenger ikke hjelp fra andre eller et ganghjelpemiddel (stokk eller rullator) på grunn av tilstivning.
2: Mild:	Jeg stivner til og har problemer med å begynne å gå igjen, men jeg trenger ikke hjelp fra andre eller et ganghjelpemiddel (stokk eller rullator) på grunn av tilstivning.
3: Moderat:	Når jeg stivner til har jeg store problemer med å begynne å gå igjen, og på grunn av tilstivning trenger jeg av og til å bruke et ganghjelpemiddel eller hjelp fra andre.
4: Alvorlig:	På grunn av tilstivning trenger jeg et ganghjelpemiddel eller hjelp av noen mesteparten eller hele tiden.

Dette er slutten på spørreskjemaet. Det kan hende vi har spurt om problemer du ikke har, og kanskje har vi nevnt problemer du aldri vil få. Ikke alle pasienter får alle disse problemene, men fordi de kan forekomme er det viktig å stille alle disse spørsmålene til alle pasienter. Tusen takk for at du brukte tid og oppmerksomhet på å fullføre dette spørreskjemaet.

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Part III: Motor Examination

Overview: This portion of the scale assesses the motor signs of PD. In administering Part III of the MDS-UPDRS the examiner should comply with the following guidelines:

At the top of the form, mark whether the patient is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.

Also, if the patient is receiving medication for treating the symptoms of Parkinson's disease, mark the patient's clinical state using the following definitions:

ON is the typical functional state when patients are receiving medication and have a good response.
OFF is the typical functional state when patients have a poor response in spite of taking medications.

The investigator should "rate what you see." Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation "**UR**" for Unable to Rate. Otherwise, rate the performance of each task as the patient performs in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the patient is to perform and rates function immediately thereafter. For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.17), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether these movements interfered with the motor examination.

3a Is the patient on medication for treating the symptoms of Parkinson's disease? ☐ No ☐ Yes

3b If the patient is receiving medication for treating the symptoms of Parkinson's disease, mark the patient's clinical state using the following definitions:

☐ ON: On is the typical functional state when patients are receiving medication and have a good response.

☐ OFF: Off is the typical functional state when patients have a poor response in spite of taking medications.

3c Is the patient on levodopa ? ☐ No ☐ Yes

3.C1 If yes, minutes since last levodopa dose: _____

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	SCORE
3.1 SPEECH Instructions to examiner: Listen to the patient's free-flowing speech and engage in conversation if necessary. Suggested topics: ask about the patient's work, hobbies, exercise, or how he got to the doctor's office. Evaluate volume, modulation (prosody) and clarity, including slurring, palilalia (repetition of syllables), and tachyphemia (rapid speech, running syllables together). 0: Normal: No speech problems. 1: Slight: Loss of modulation, diction, or volume, but still all words easy to understand. 2: Mild: Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow. 3: Moderate: Speech is difficult to understand to the point that some, but not most, sentences are poorly understood. 4: Severe: Most speech is difficult to understand or unintelligible.	☐
3.2 FACIAL EXPRESSION Instructions to examiner: Observe the patient sitting at rest for 10 seconds, without talking and also while talking. Observe eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling, and parting of lips. 0: Normal: Normal facial expression. 1: Slight: Minimal masked facies manifested only by decreased frequency of blinking. 2: Mild: In addition to decreased eye-blink frequency, masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted. 3: Moderate: Masked facies with lips parted some of the time when the mouth is at rest. 4: Severe: Masked facies with lips parted most of the time when the mouth is at rest.	☐

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	SCORE
3.3 RIGIDITY Instructions to examiner: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity. 0: Normal: No rigidity. 1: Slight: Rigidity only detected with activation maneuver. 2: Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved. 3: Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort. 4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.	☐ Neck ☐ RUE ☐ LUE ☐ RLE ☐ LLE
3.4 FINGER TAPPING Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps. 2: Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence. 3: Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.	☐ R ☐ L

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	SCORE
3.5 HAND MOVEMENTS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.	☐ R ☐ L
3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down, and then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st supination-pronation sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.	☐ R ☐ L

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	SCORE
3.7 TOE TAPPING Instructions to examiner: Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps. 2: Mild: Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the 1st tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L
3.8 LEG AGILITY Instructions to examiner: Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the 1st tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.	☐ R ☐ L

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	SCORE
3.9 ARISING FROM CHAIR Instructions to examiner: Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt up to a maximum of two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13. 0: Normal: No problems. Able to arise quickly without hesitation. 1: Slight: Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair. 2: Mild: Pushes self up from the arms of the chair without difficulty. 3: Moderate: Needs to push off, but tends to fall back; or may have to try more than one time using the arms of the chair, but can get up without help. 4: Severe: Unable to arise without help.	☐
3.10 GAIT Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for "freezing of gait" (next item 3.11) while patient is walking. Observe posture for item 3.13. 0: Normal: No problems. 1: Slight: Independent walking with minor gait impairment. 2: Mild: Independent walking but with substantial gait impairment. 3: Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person. 4: Severe: Cannot walk at all or only with another person's assistance.	☐

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	SCORE
3.11 FREEZING OF GAIT Instructions to examiner: While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movements especially when turning and reaching the end of the task. To the extent that safety permits, patients may NOT use sensory tricks during the assessment. 0: Normal: No freezing. 1: Slight: Freezes on starting, turning, or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking. 2: Mild: Freezes on starting, turning, or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking. 3: Moderate: Freezes once during straight walking. 4: Severe: Freezes multiple times during straight walking.	☐
3.12 POSTURAL STABILITY Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test retropulsion. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the center of gravity so that patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the examiner feels reflects the patient's limitations rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13. 0: Normal: No problems. Recovers with one or two steps. 1: Slight: 3-5 steps, but subject recovers unaided. 2: Mild: More than 5 steps, but subject recovers unaided. 3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner. 4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.	☐

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	SCORE
3.13 POSTURE Instructions to examiner: Posture is assessed with the patient standing erect after arising from a chair, during walking, and while being tested for postural reflexes. If you notice poor posture, tell the patient to stand up straight and see if the posture improves (see option 2 below). Rate the worst posture seen in these three observation points. Observe for flexion and side-to-side leaning. 0: Normal: No problems. 1: Slight: Not quite erect, but posture could be normal for older person. 2: Mild: Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so. 3: Moderate: Stooped posture, scoliosis or leaning to one side that cannot be corrected volitionally to a normal posture by the patient. 4: Severe: Flexion, scoliosis or leaning with extreme abnormality of posture.	☐
3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA) Instructions to examiner: This global rating combines all observations on slowness, hesitancy, and small amplitude and poverty of movement in general, including a reduction of gesturing and of crossing the legs. This assessment is based on the examiner's global impression after observing for spontaneous gestures while sitting, and the nature of arising and walking. 0: Normal: No problems. 1: Slight: Slight global slowness and poverty of spontaneous movements. 2: Mild: Mild global slowness and poverty of spontaneous movements. 3: Moderate: Moderate global slowness and poverty of spontaneous movements. 4: Severe: Severe global slowness and poverty of spontaneous movements.	☐
3.15 POSTURAL TREMOR OF THE HANDS Instructions to examiner: All tremor, including re-emergent rest tremor, that is present in this posture is to be included in this rating. Rate each hand separately. Rate the highest amplitude seen. Instruct the patient to stretch the arms out in front of the body with palms down. The wrist should be straight and the fingers comfortably separated so that they do not touch each other. Observe this posture for 10 seconds. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L

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	SCORE
3.16 KINETIC TREMOR OF THE HANDS Instructions to examiner: This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L
3.17 REST TREMOR AMPLITUDE Instructions to examiner: This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking, and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor. As part of this rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/jaw. Rate only the maximum amplitude that is seen at any time as the final rating. Extremity ratings 0: Normal: No tremor. 1: Slight: < 1 cm in maximal amplitude. 2: Mild: ≥ 1 cm but < 3 cm in maximal amplitude. 3: Moderate: ≥ 3 cm but < 10 cm in maximal amplitude. 4: Severe: ≥ 10 cm in maximal amplitude. Lip/Jaw ratings 0: Normal: No tremor. 1: Slight: < 1 cm in maximal amplitude. 2: Mild: ≥ 1 cm but < 2 cm in maximal amplitude. 3: Moderate: ≥ 2 cm but < 3 cm in maximal amplitude. 4: Severe: ≥ 3 cm in maximal amplitude.	☐ RUE ☐ LUE ☐ RLE ☐ LLE ☐ Lip/Jaw

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3.18 CONSTANCY OF REST TREMOR	SCORE
Instructions to examiner: This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variously at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating. 0: Normal: No tremor. 1: Slight: Tremor at rest is present ≤ 25% of the entire examination period. 2: Mild: Tremor at rest is present 26-50% of the entire examination period. 3: Moderate: Tremor at rest is present 51-75% of the entire examination period. 4: Severe: Tremor at rest is present > 75% of the entire examination period.	☐

DYSKINESIA IMPACT ON PART III RATINGS	
A. Were dyskinesias (chorea or dystonia) present during examination?	☐ No ☐ Yes
B. If yes, did these movements interfere with your ratings?	☐ No ☐ Yes

HOEHN AND YAHR STAGE	
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.	☐

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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 the patient is generally awake 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 mediation 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]

SCORE

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 calculations).

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): _____

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	SCORE
4.2 FUNCTIONAL IMPACT OF DYSKINESIAS 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. *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?* 0: Normal: No dyskinesias or no impact by dyskinesias on activities or social interactions. 1: Slight: Dyskinesias impact on a few activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods. 2: Mild: Dyskinesias impact on many activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods. 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. 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.	☐
B. MOTOR FLUCTUATIONS	
4.3 TIME SPENT IN THE OFF STATE 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. *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).* 0: Normal: No OFF time. 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 OFF: _____ 3. % OFF = ((2/1)*100): _____	☐

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	SCORE
4.4 FUNCTIONAL IMPACT OF FLUCTUATIONS Instructions to examiner: 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. *Instructions to patient [and caregiver]: 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?* 0: Normal: No fluctuations or no impact by fluctuations on performance of activities or social interactions. 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. 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. 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. 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.	☐
4.5 COMPLEXITY OF MOTOR FLUCTUATIONS Instructions to examiner: 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 caregivers 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. *Instructions to patient [and caregiver]: 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 always come at a certain time? Do they mostly come at a certain time? Do they only sometimes come at a certain time? Are your low periods totally unpredictable?"* 0: Normal: No motor fluctuations. 1: Slight: OFF times are predictable all or almost all of the time (> 75%). 2: Mild: OFF times are predictable most of the time (51-75%). 3: Moderate: OFF times are predictable some of the time (26-50%). 4: Severe: OFF episodes are rarely predictable (≤ 25%).	☐

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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 with 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.

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Patient Name or Subject ID	Site ID	(mm-dd-yyyy) Assessment Date	Investigator's Initials
_____	___ ___ ___	_____ - _____ - _____	___ ___ ___

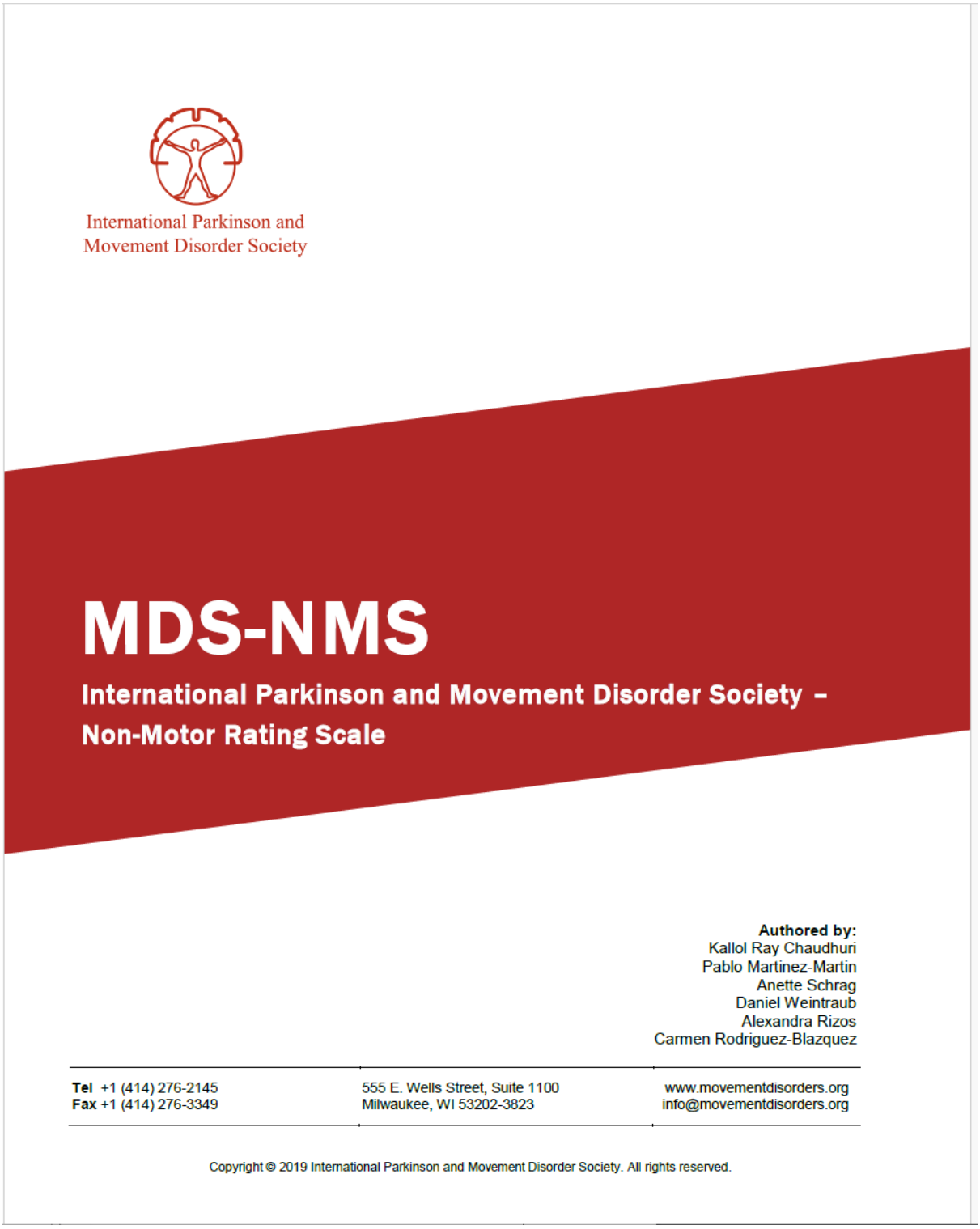
MDS UPDRS Score Sheet

1.A	Source of information	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.3b	Rigidity– RUE	
			3.3c	Rigidity– LUE	
Part I			3.3d	Rigidity– RLE	
1.1	Cognitive impairment		3.3e	Rigidity– LLE	
1.2	Hallucinations and psychosis		3.4a	Finger tapping– Right hand	
1.3	Depressed mood		3.4b	Finger tapping– Left hand	
1.4	Anxious mood		3.5a	Hand movements– Right hand	
1.5	Apathy		3.5b	Hand movements– Left hand	
1.6	Features of DDS		3.6a	Pronation- supination movements– Right hand	
1.6a	Who is filling out questionnaire	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.6b	Pronation- supination movements– Left hand	
			3.7a	Toe tapping– Right foot	
1.7	Sleep problems		3.7b	Toe tapping– Left foot	
1.8	Daytime sleepiness		3.8a	Leg agility– Right leg	
1.9	Pain and other sensations		3.8b	Leg agility– Left leg	
1.10	Urinary problems		3.9	Arising from chair	
1.11	Constipation problems		3.10	Gait	
1.12	Light headedness on standing		3.11	Freezing of gait	
1.13	Fatigue		3.12	Postural stability	
Part II			3.13	Posture	
2.1	Speech		3.14	Global spontaneity of movement	
2.2	Saliva and drooling		3.15a	Postural tremor– Right hand	
2.3	Chew ing and sw allow ing		3.15b	Postural tremor– Left hand	
2.4	Eating tasks		3.16a	Kinetic tremor– Right hand	
2.5	Dressing		3.16b	Kinetic tremor– Left hand	
2.6	Hygiene		3.17a	Rest tremor amplitude– RUE	
2.7	Handw riting		3.17b	Rest tremor amplitude– LUE	
2.8	Doing hobbies and other activities		3.17c	Rest tremor amplitude– RLE	
2.9	Turning in bed		3.17d	Rest tremor amplitude– LLE	
2.10	Tremor		3.17e	Rest tremor amplitude– Lip/jaw	
2.11	Getting out of bed		3.18	Constancy of rest tremor	
2.12	Walking and balance			Were dyskinesias present?	☐ No ☐ Yes
2.13	Freezing			Did these movements interfere w ith ratings?	☐ No ☐ Yes
3a	Is the patient on medication?	☐ No ☐ Yes		Hoehn and Yahr Stage	
3b	Patient's clinical state	☐ Off ☐ On	**Part IV**		
3c	Is the patient on levodopa?	☐ No ☐ Yes	4.1	Time spent w ith dyskinesias	
3.C1	If yes, minutes since last dose:		4.2	Functional impact of dyskinesias	
Part III			4.3	Time spent in the OFF state	
3.1	Speech		4.4	Functional impact of fluctuations	
3.2	Facial expression		4.5	Complexity of motor fluctuations	
3.3a	Rigidity– Neck		4.6	Painful OFF-state dystonia	

3 MDS-NMS

International Parkinson and Movement Disorder Society – Non-Motor Rating Scale

MDS-NMS - Page 1



International Parkinson and
Movement Disorder Society

MDS-NMS

International Parkinson and Movement Disorder Society –
Non-Motor Rating Scale

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MDS-NMS - Page 2

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MDS-NMS – Page 3

International Parkinson and Movement Disorder Society –
Non-Motor Rating Scale (MDS-NMS)

RATER-ADMINISTERED VERSION

Rate symptoms over past 4 weeks

Patient Name or Identifier: _____

Date: _____

Respondent: ☐ Patient ☐ Informant/Caregiver ☐ Patient and Informant

Patient's motor state: ☐ On ☐ Off

SCORING

Average Frequency / Duration: (percentages denote days per week or hours per waking day)

0:	Never	
1:	Rarely	(≤ 10% of time)
2:	Sometimes	(11-25% of time)
3:	Frequently	(26-50% of time)
4:	Majority of time	(≥ 51% of time)

Average Severity:

0:	Not present	(only if frequency = 0)
1:	Minimal	(no distress or disturbance to patient or caregiver)
2:	Mild	(minor distress or disturbance to patient or caregiver)
3:	Moderate	(considerable distress or disturbance to patient or caregiver)
4:	Severe	(major distress or disturbance to patient or caregiver)

Calculations:

Item Total	**= Frequency multiplied by severity**
Subscale Total	**= Sum of all Item totals for that Subscale**
MDS-NMS Total Score	**= Sum of totals for Subscales A-M**

For each question use the following introduction:
"How often have you..." or **"How often has the patient..."**

If the answer to the question is "Never", rate frequency/duration as "0", rate severity also as "0" and move on to the next question.

If the answer to the question is not "Never", then ask:
"When you have had… / When the patient has had… [the symptom], how bad has it been on average?"

When answering questions about an **"increase"** or **"decrease"/"reduction"** in symptoms, use as your comparison point your/the patient's experiences on average as an adult prior to having Parkinson's disease.

MDS-NMS – Page 4

International Parkinson and Movement Disorder Society – Non-Motor Rating Scale (MDS-NMS)

RATER-ADMINISTERED VERSION

Rate symptoms over past 4 weeks

	Frequency (0-4)	Severity (0-4)	Frequency x severity
A. Depression:			
1. Felt sad or depressed?			
2. Had difficulty experiencing pleasure?			
3. Felt hopeless?			
4. Had negative thoughts about yourself?			
5. Felt that life is not worth living?			
Subscale A Total			
B. Anxiety:			
1. Felt worried?			
2. Felt nervous?			
3. Had panic or anxiety attacks?			
4. Been worried about being in public or in social situations?			
Subscale B Total			
C. Apathy:			
1. Had a reduced motivation to start day-to-day activities?			
2. Had a reduced interest in talking to people?			
3. Had a reduction in experiencing emotions?			
Subscale C Total			
D. Psychosis:			
1. Sensed things or people in margins of your visual field? (passage or presence phenomena)			
2. Visually misinterpreted an actual object? (illusions)			
3. Seen, heard, felt, tasted, or smelled things that other people did not? (hallucinations)			
4. Believed things to be true that others did not? (e.g., delusions of persecution, jealousy, or misidentification)			
Subscale D Total			
E. Impulse Control and Related Disorders:			
1. Had an increase in gambling, sexual, buying, or eating behaviors?			
2. Had an increase in other behaviors (e.g., internet use, hobbies, artistic activities, writing, hoarding)?			
3. Repeatedly handled objects without any purpose? (punding)			
4. Routinely taken more anti-parkinsonian medications than prescribed? (dopamine dysregulation syndrome)			
Subscale E Total			

MDS-NMS – Page 5

International Parkinson and Movement Disorder Society – Non-Motor Rating Scale (MDS-NMS)

RATER-ADMINISTERED VERSION

Rate symptoms over past 4 weeks

	Frequency (0-4)	Severity (0-4)	Frequency x severity
F. Cognition:			
1. Had difficulty remembering things?			
2. Had difficulty learning new things?			
3. Had difficulty keeping focus or paying attention?			
4. Had difficulty finding words or expressing ideas?			
5. Had difficulty planning or carrying out complex tasks, not due to motor problems? (executive abilities)			
6. Had difficulty judging the position of things? (visuospatial abilities)			
Subscale F Total			
G. Orthostatic Hypotension:			
1. Felt lightheaded or fainted when changing position?			
2. Had dizziness or weakness upon standing?			
Subscale G Total			
H. Urinary:			
1. Had an urgent need to empty bladder? (urinary urgency)			
2. Had to empty bladder more than every 2 hours? (urinary frequency)			
3. Had to empty bladder more than twice overnight? (nocturia)			
Subscale H Total			
I. Sexual:			
1. Had decreased sexual drive or interest in sex?			
2. Had difficulty with sexual arousal (e.g., erectile dysfunction or vaginal dryness) or sexual performance not related to motor problems (e.g., not related to Parkinson's rigidity)?			
Subscale I Total			
J. Gastrointestinal:			
1. Had any drooling of saliva?			
2. Had difficulty swallowing?			
3. Had nausea or felt sick in the stomach?			
4. Had constipation? (defined as < 3 bowel movements/week)			
Subscale J Total			

MDS-NMS – Page 6

International Parkinson and Movement Disorder Society – Non-Motor Rating Scale (MDS-NMS)

RATER-ADMINISTERED VERSION

Rate symptoms over past 4 weeks

	Frequency (0-4)	Severity (0-4)	Frequency x severity
K. Sleep and Wakefulness:			
1. Had difficulty falling asleep or staying asleep? (insomnia)			
2. Acted out dreams while asleep, such as shouting, flailing arms, punching, or running movements? (REM sleep behavior)			
3. Dozed off or fallen asleep unintentionally during waking hours? (e.g., during conversation, at mealtimes, or while driving, watching television; excessive daytime sleepiness)			
4. Had an irresistible urge to move legs or arms when sitting or lying down which improved with movement? (restlessness)			
5. Had any involuntary jerky movements in arms or legs during sleep or while resting? (periodic limb movements)			
6. Woken at night due to snoring, gasping, or difficulty with breathing?			
	Subscale K Total		
L. Pain:			
1. Had muscle, joint, or back pain?			
2. Had a deep or dull aching pain within the body?			
3. Had pain due to abnormal twisting movements of arms or legs or body, often present in the early morning period? (dystonia)			
4. Had other types of pain? (e.g., nocturnal pain, orofacial pain)			
	Subscale L Total		
M. Other:			
1. Had an unintentional weight loss? (rate frequency as either not present (0) or present (4); for severity rate 0 (only if frequency = 0), 1 (minimal), 2 (mild), 3 (moderate), or 4 (severe))			
2. Had a decrease in sense of smell? (impaired olfaction) (rate frequency as either not present (0) or present (4); for severity rate 0 (only if frequency = 0), 1 (minimal), 2 (mild), 3 (moderate), or 4 (severe))			
3. Felt excessively physically tired? (physical fatigue)			
4. Felt excessively mentally tired? (mental fatigue)			
5. Had excessive sweating not related to temperature?			
	Subscale M Total		

MDS-NMS TOTAL SCORE	

MDS-NMS – Page 7

International Parkinson and Movement Disorder Society –
Non-Motor Rating Scale (MDS-NMS)

RATER-ADMINISTERED VERSION

Rate symptoms over past 4 weeks

MDS-NMS Non-Motor Fluctuations (NMF) Subscale

Do you / Does the patient experience changes in non-motor symptoms (as listed below) in relation to the timing of anti-parkinsonian medications (i.e., symptoms occurring or worsening during "Off" period)?

☐ Yes ☐ No

If no, MDS-NMS NMF Total Score (below) = 0

If yes, please complete the following section:

SCORING

Typical degree of change from "On" to "Off" period:

0: No change
1: Minimal
2: Small
3: Medium
4: Large

Subscore "Change" **= Sum of all "Degree of change" items**

MDS-NMS NMF Total Score **= Subscore "Change" multiplied by Subscore "Time"**

	Degree of change (0-4)
1. Depression (as listed in Subscale A)	
2. Anxiety (as listed in Subscale B)	
3. Thinking or cognitive abilities (as listed in Subscale F)	
4. Bladder symptoms (as listed Subscale H)	
5. Restlessness (as listed in Subscale K, item 4)	
6. Pain (as listed in Subscale L)	
7. Fatigue (as listed in Subscale M, items 3 and 4)	
8. Excessive sweating (as listed in Subscale M, item 5)	

Time spent in non-motor "Off" state:

1: Rarely (≤ 10% of waking day)
2: Sometimes (11-25% of waking day)
3: Frequently (26-50% of waking day)
4: Majority of time (≥ 51% of waking day)

MDS-NMS NMF Subscore "Change"	
MDS-NMS NMF Subscore "Time"	
MDS-NMS NMF Total Score (Subscore "Change" x "Time")	

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MDS-NMS – Page 8

Patient Name/Identifier: _____ Date: _____

MDS-NMS Score Sheet

RATER-ADMINISTERED VERSION

Item Total = Frequency multiplied by Severity
Subscale Total = Sum of all Item Totals for that Subscale
MDS-NMS Total Score = Sum of Totals for Subscales A-M

Respondent: ☐ Patient ☐ Informant/Caregiver ☐ Patient and Informant

Patient's motor state: ☐ On ☐ Off

A. Depression	Frequency	Severity	Total
1. Sad or depressed			
2. Experiencing pleasure			
3. Hopelessness			
4. Negative thoughts			
5. Life not worth living			
Depression Subscale Total			

B. Anxiety	Frequency	Severity	Total
1. Worried			
2. Nervous			
3. Panic or anxiety attacks			
4. Social phobia			
Anxiety Subscale Total			

C. Apathy	Frequency	Severity	Total
1. Interest activities			
2. Interest talking			
3. Emotions			
Apathy Subscale Total			

D. Psychosis	Frequency	Severity	Total
1. Passage or presence phenomena			
2. Illusions			
3. Hallucinations			
4. Delusions			
Psychosis Subscale Total			

E. Impulse Control and Related Disorders	Frequency	Severity	Total
1. Impulse control disorders			
2. Other compulsive behaviors			
3. Punding			
4. Dopamine dysregulation syndrome			
Impulse Control and Related Disorders Subscale Total			

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MDS-NMS – Page 9

Patient Name/Identifier: _____ Date: _____

F. Cognition	Frequency	Severity	Total
1. Remembering			
2. Learning new information			
3. Focus or attention			
4. Find words or express ideas			
5. Executive abilities			
6. Visuospatial abilities			
Cognition Subscale Total			

G. Orthostatic Hypotension	Frequency	Severity	Total
1. Lightheaded or fainted			
2. Dizziness or weakness			
Orthostatic Hypotension Subscale Total			

H. Urinary	Frequency	Severity	Total
1. Urinary urgency			
2. Urinary frequency			
3. Nocturia			
Urinary Subscale Total			

I. Sexual	Frequency	Severity	Total
1. Sex drive or interest			
2. Sexual arousal or performance			
Sexual Subscale Total			

J. Gastrointestinal	Frequency	Severity	Total
1. Drooling			
2. Swallowing			
3. Nausea or sick in stomach			
4. Constipation			
Gastrointestinal Subscale Total			

K. Sleep and Wakefulness	Frequency	Severity	Total
1. Insomnia			
2. REM sleep behavior			
3. Dozing off			
4. Restlessness			
5. Periodic limb movements			
6. Snoring or difficulty breathing			
Sleep and Wakefulness Subscale Total			

 7

MDS-NMS – Page 10

Patient Name/Identifier: _____ Date: _____

L. Pain	Frequency	Severity	Total
1. Muscle, joint, back pain			
2. Deep or dull pain			
3. Dystonia			
4. Other pain			
Pain Subscale Total			

M. Other	Frequency	Severity	Total
1. Weight loss			
2. Decreased smell			
3. Physical fatigue			
4. Mental fatigue			
5. Excessive sweating			
Other Subscale Total			

MDS-NMS TOTAL SCORE	

MDS-NMS Score Sheet – Non Motor Fluctuations
Subscore "Change" = Sum of all "degree of change" items
Subscore "Time" = Time spent in non-motor "Off" state
MDS-NMS NMF Total Score = Subscore "Change" multiplied by Subscore "Time"

NON-MOTOR FLUCTUATIONS (optional)	Typical degree of change from "On" to "Off" period
1. Depression	
2. Anxiety	
3. Thinking or cognitive abilities	
4. Bladder symptoms	
5. Restlessness	
6. Pain	
7. Fatigue	
8. Excessive sweating	
Subscore "Change"	

Subscore "Time"	

MDS-NMS NON-MOTOR FLUCTUATIONS TOTAL SCORE	

MDS-NMS – Page 11

International Parkinson and Movement Disorder Society –
Non-Motor Rating Scale (MDS-NMS)

Glossary of Terms

A. **Depression**: a mood disorder characterized by sustained change in emotions (sadness, decreased interest or pleasure), cognition (negative thoughts about life or self, such as hopelessness, helplessness, indecisiveness, or death or suicide ideation) or behavior (isolative, withdrawn, sleep disturbances, appetite disturbances)

B. **Anxiety**: an affective disorder characterized by sustained excessive worrying which can be (1) generalized and include symptoms such as restlessness, being easily fatigued, mind going blank or trouble concentrating, irritability, and muscle tension; (2) specific anxiety or panic attacks; (3) fear of being in public (agoraphobia); or (4) fear of being in social situations (social phobia)
   Anxiety or panic attack: an abrupt surge of intense fear or intense discomfort, can include shortness of breath, heart beating fast, upset stomach, sweating, dizziness or faintness, sensation of chill or heat, or sense something bad is going to happen or even a sense of dying

C. **Apathy**: a disorder characterized by decreased motor activity (less initiation of motor activity not due to parkinsonism), emotional expression (less emotional engagement separate from decreased facial expression due to parkinsonism), or speech (less likely to initiate or engage in conversation)

D. **Psychosis**: a disorder characterized by changes in perception (passage or presence phenomena, illusions, or hallucinations) or thought (delusions)
   Passage phenomenon: visual sensation of something moving in periphery of visual field
   Presence phenomenon: visual sensation of person being in periphery of visual field
   Illusions: visual misinterpretation of an actual object
   Hallucinations: a sensory (visual, auditory, taste, smell, or feeling) experience that is not real or experienced by other people
   Delusions: a belief that something is true for which there is no objective evidence and which other persons do not hold true

E. **Impulse control disorders**: a failure to resist an impulse or drive that leads to repeated engagement in activities that become harmful to self or others; compared with pre-PD behavior
   Hoarding: the needless collection of objects and an inability to get rid of them
   Punding: the needless or purposeless repetition of a simple motor activity
   Dopamine dysregulation syndrome: taking an excess (beyond what is prescribed) of Parkinson's disease medications for their motor or psychological effects, often with significant mood changes during "on" (irritability, hypomania) or "off" (dysphoria) states

F. **Cognition**: the activities of thinking, understanding, learning, and remembering
   Attention: concentrating on one part of the environment while ignoring other things
   Executive abilities: cognitive processes involved in maintaining multiple pieces of information in the mind at the same time, reasoning, task flexibility, problem solving, and task planning and execution
   Visuospatial abilities: ability relating to visual perception of spatial relationships among objects

MDS-NMS – Page 12

International Parkinson and Movement Disorder Society –
Non-Motor Rating Scale (MDS-NMS)

G. **Orthostatic hypotension**: a drop in blood pressure severe enough to cause symptoms when changing from sitting to standing position or from lying to sitting position

H. **Urinary**
Nocturia: excessive urination at night, defined as more than 2 times overnight

I. **Sexual**
Erectile dysfunction: inability of a man to maintain an erection sufficient for satisfying sexual activity

J. **Gastrointestinal**: relating to the stomach and intestines
Saliva: watery liquid secreted into the mouth by glands, providing lubrication for chewing and swallowing, and aiding digestion
Swallowing: difficulty swallowing including liquids and solids, as well as choking while swallowing
Nausea: a feeling of sickness with a tendency to vomit
Constipation: infrequent bowel movements (usually less than three bowel movements per week) or difficult passage of stools

K. **Sleep and wakefulness**
Insomnia: difficultly falling asleep or staying asleep
Rapid eye movement (REM) sleep: a stage in the normal sleep cycle during which dreams occur and the body undergoes marked changes including rapid eye movement, loss of reflexes, and increased pulse rate and brain activity

L. **Pain**
Dystonia: a state of abnormal muscle tone resulting in muscular spasm and abnormal posture
Nocturnal pain: pain overnight
Orofacial pain: pain which is felt in the mouth, jaws, or face

M. **Other**
Olfaction: the action or capacity of smelling
Fatigue (physical): state of excessive physical weariness or exhaustion (after physical exertion), different from sleepiness
Fatigue (mental): state of excessive mental weariness or exhaustion, different from sleepiness

4 MODIFIED GIDS-PD

The Gastrointenstinal Dysfunction Scale for Parkinson's Disease modified*

The following version of GIDS-PD has been modified by permission and license from MDS for use in the N-DOSE trial. The modifications in this version is that the timeframe for all questions has been reduced from six months to one month. Part 1b has also been omitted from the scale.

Modified GIDS-PD – Page 1

International Parkinson and Movement Disorder Society

GIDS-PD modified*

The Gastrointestinal Dysfunction Scale for Parkinson's Disease

*by permission and license from MDS for use in the N-DOSE trial.

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Modified GIDS-PD – Page 2

GIDS-PD modified*

THE GASTROINTESTINAL DYSFUNCTION SCALE IN PARKINSON'S DISEASE

*by permission and license from MDS for use in the N-DOSE trial.

INSTRUCTIONS

Some patients with Parkinson's disease experience changes in their digestive system. This questionnaire assesses whether you have experienced any gut problems. Tick the statement that best describes your symptoms over the **past month** . Be sure to read all the statements in each item.

If you have had the problem in the past but have not experienced the problem in the **past month** , please tick 'No'.

If you have used medication in the **past month** related to any of the following problems, answer about your experience while taking the medication.

Please answer every question. If you are uncertain about how to answer a question tick the statement that best describes your symptoms.

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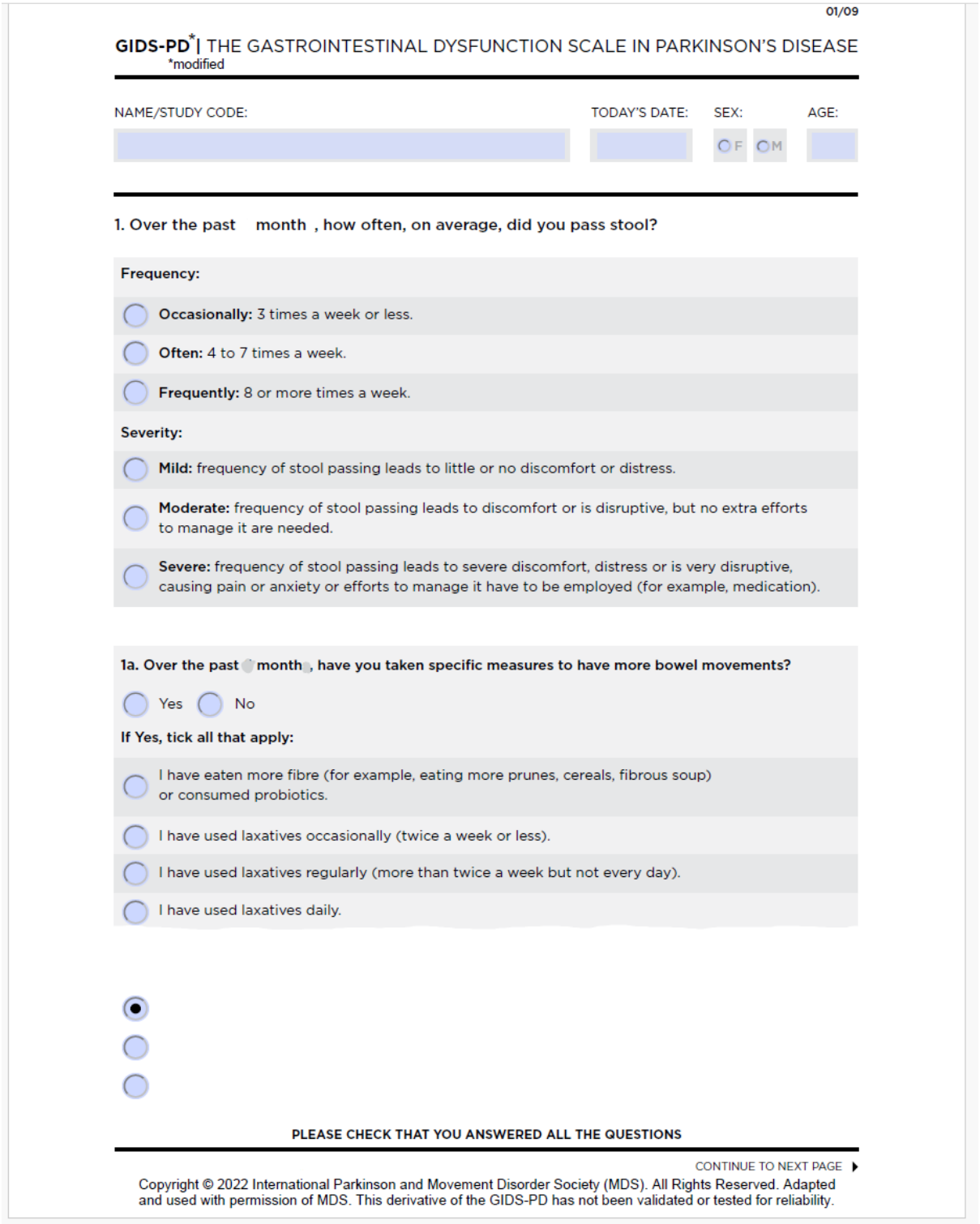
Modified GIDS-PD – Page 3



01/09

GIDS-PD* | THE GASTROINTESTINAL DYSFUNCTION SCALE IN PARKINSON'S DISEASE
*modified

NAME/STUDY CODE: TODAY'S DATE: SEX: ○F ○M AGE:

1. Over the past month , how often, on average, did you pass stool?

Frequency:

- ○ **Occasionally:** 3 times a week or less.
- ○ **Often:** 4 to 7 times a week.
- ○ **Frequently:** 8 or more times a week.

Severity:

- ○ **Mild:** frequency of stool passing leads to little or no discomfort or distress.
- ○ **Moderate:** frequency of stool passing leads to discomfort or is disruptive, but no extra efforts to manage it are needed.
- ○ **Severe:** frequency of stool passing leads to severe discomfort, distress or is very disruptive, causing pain or anxiety or efforts to manage it have to be employed (for example, medication).

1a. Over the past month, have you taken specific measures to have more bowel movements?

○ Yes ○ No

If Yes, tick all that apply:

- ○ I have eaten more fibre (for example, eating more prunes, cereals, fibrous soup) or consumed probiotics.
- ○ I have used laxatives occasionally (twice a week or less).
- ○ I have used laxatives regularly (more than twice a week but not every day).
- ○ I have used laxatives daily.

●
○
○

PLEASE CHECK THAT YOU ANSWERED ALL THE QUESTIONS

CONTINUE TO NEXT PAGE ▸

Modified GIDS-PD – Page 4

GIDS-PD* | THE GASTROINTESTINAL DYSFUNCTION SCALE IN PARKINSON'S DISEASE
*modified

2. Over the past month , have you experienced straining (difficulty passing stool, finding it painful to pass stool)?

◯ Yes ◯ No

If Yes,
Frequency:

◯ **Occasionally:** once every 10 times I go to the toilet, or less.

◯ **Often:** on average, once every 4 times I go to the toilet.

◯ **Frequently:** at least one in every 2 times I go to the toilet.

Severity:

◯ **Mild:** straining is present but leads to little or no discomfort or distress.

◯ **Moderate:** straining leads to discomfort or is disruptive (for example, it delays stool passing, takes increased effort to pass stool, or you have piles because of straining).

◯ **Severe:** straining leads to severe discomfort, distress or is very disruptive, causing pain or anxiety or efforts to manage it have to be employed (for example, you had to press on or around your bottom, remove stool with your hands, or have enemas).

3. Over the past month , have you experienced hard stools?

◯ Yes ◯ No

If Yes,
Frequency:

◯ **Occasionally:** once every 10 times I go to the toilet, or less.

◯ **Often:** on average, once every 4 times I go to the toilet.

◯ **Frequently:** at least once in every 2 times I go to the toilet.

Severity:

◯ **Mild:** hard stools are present but lead to little or no discomfort or distress.

◯ **Moderate:** hard stools lead to discomfort or are very disruptive (for example, it takes increased effort to pass stool).

◯ **Severe:** hard stools lead to severe discomfort, distress or are very disruptive, causing pain or anxiety.

PLEASE CHECK THAT YOU ANSWERED ALL THE QUESTIONS

CONTINUE TO NEXT PAGE ▸

Modified GIDS-PD – Page 5

03/09

GIDS-PD* | THE GASTROINTESTINAL DYSFUNCTION SCALE IN PARKINSON'S DISEASE
*modified

4. Over the past month , have you experienced a sensation of incomplete evacuation?

◯ Yes ◯ No

If Yes,
Frequency:

- ◯ **Occasionally:** once every 10 times I go to the toilet, or less.
- ◯ **Often:** on average, once every 4 times I go to the toilet.
- ◯ **Frequently:** at least once in every 2 times I go to the toilet.

Severity:

- ◯ **Mild:** sensation of incomplete evacuation is present but leads to little or no discomfort or distress.
- ◯ **Moderate:** sensation of incomplete evacuation leads to discomfort or is disruptive (delaying passing of stool).
- ◯ **Severe:** sensation of incomplete evacuation leads to severe discomfort, distress or is very disruptive, causing pain or anxiety or efforts to manage it have to be employed (for example, prompting several attempts to pass stool on that day).

---

5. Over the past month , have you experienced abdominal pain?

◯ Yes ◯ No

If Yes,
Frequency:

- ◯ **Occasionally:** less than once a week.
- ◯ **Often:** on average, once a week.
- ◯ **Frequently:** at least twice a week.

Severity:

- ◯ **Mild:** abdominal pain is present but leads to little or no discomfort or distress.
- ◯ **Moderate:** abdominal pain leads to discomfort or is disruptive.
- ◯ **Severe:** abdominal pain leads to severe discomfort, distress or is very disruptive and stops you from doing your activities.

PLEASE CHECK THAT YOU ANSWERED ALL THE QUESTIONS

CONTINUE TO NEXT PAGE ▸

Modified GIDS-PD – Page 6

04/09

GIDS-PD*| THE GASTROINTESTINAL DYSFUNCTION SCALE IN PARKINSON'S DISEASE
*modified

6. Over the past month , have you experienced days in which you have had an abnormal increase in stool passing? If you experienced constipation on some days but you also experienced increased frequency of stool passing, please tick yes.

Yes No

If Yes,
Frequency:

- **Occasionally:** less than once a week, I have needed to pass a stool more often than usual.
- **Often:** on average, once a week, I have needed to pass a stool more often than usual.
- **Frequently:** at least twice a week, I have needed to pass a stool more often than usual.

Severity:

- **Mild:** increased frequency of stool passing is present but leads to little or no discomfort or distress.
- **Moderate:** increased frequency of stool passing leads to discomfort or is disruptive.
- **Severe:** increased frequency of stool passing leads to severe discomfort, distress or is very disruptive and stops you from doing your activities (for example, faecal incontinence).

---

7. Over the past month , have you experienced abdominal fullness, pressure, or a sensation of trapped gas, feeling bloated or distension (visible increase in abdominal girth)?

Yes No

If Yes,
Frequency:

- **Occasionally:** less than once a week.
- **Often:** on average, once a week.
- **Frequently:** at least twice a week.

Severity:

- **Mild:** recurrent abdominal fullness is present but leads to little or no discomfort or distress.
- **Moderate:** recurrent abdominal fullness leads to discomfort or is disruptive (for example, feeling excessively full after regular-sized meals).
- **Severe:** recurrent abdominal fullness leads to severe discomfort, distress or is very disruptive and stops you from doing your activities or eating plentiful meals.

PLEASE CHECK THAT YOU ANSWERED ALL THE QUESTIONS

CONTINUE TO NEXT PAGE ▸

Modified GIDS-PD – Page 7

05/09

GIDS-PD* | THE GASTROINTESTINAL DYSFUNCTION SCALE IN PARKINSON'S DISEASE
*modified

8. Over the past month , have you experienced involuntary weight loss?
Even if you have lost weight over the course of several months and maintained this loss over the past month, please tick yes.

Yes No

If Yes,
Quantity:

- Less than 10% of my body weight.
- On average, 10% of my body weight.
- More than 10% of my body weight.

Severity:

- **Mild:** weight loss is present but leads to little or no discomfort or distress.
- **Moderate:** weight loss leads to discomfort or is disruptive.
- **Severe:** weight loss leads to severe discomfort, distress or is very disruptive (for example, you have to take nutritional supplements or appetite stimulants to manage it, or it causes frailty).

---

9. Over the past month , have you experienced difficulty swallowing or did food or drinks get stuck in your throat after swallowing or go down slowly through your chest?

Yes No

If Yes,
Frequency:

- **Occasionally:** less than once a week.
- **Often:** on average, once a week.
- **Frequently:** at least twice a week.

Severity:

- **Mild:** difficulty swallowing is present but leads to little or no discomfort or distress.
- **Moderate:** difficulty swallowing leads to discomfort or is disruptive (for example, you cut your food or pills in smaller pieces so that they are easier to swallow).
- **Severe:** difficulty swallowing leads to severe discomfort, distress or is very disruptive and stops you from eating certain foods, or you have choked in the past month.

PLEASE CHECK THAT YOU ANSWERED ALL THE QUESTIONS

CONTINUE TO NEXT PAGE ▸

Modified GIDS-PD – Page 8

GIDS-PD* | THE GASTROINTESTINAL DYSFUNCTION SCALE IN PARKINSON'S DISEASE
*modified

10. Over the past month , have you experienced excessive saliva?

Yes No

If Yes,
Frequency:

- **Occasionally:** less than once a week.
- **Often:** on average, once a week.
- **Frequently:** at least twice a week.

Severity:

- **Mild:** excessive saliva is present but leads to little or no discomfort or distress.
- **Moderate:** excessive saliva leads to discomfort or is disruptive (for example, it causes drooling).
- **Severe:** excessive saliva leads to severe discomfort, distress or is very disruptive (for example, you have to take medication to manage it, you have to keep cleaning yourself or it causes embarrassment).

11. Over the past month , have you experienced heartburn?

Yes No

If Yes,
Frequency:

- **Occasionally:** less than once a week.
- **Often:** on average, once a week.
- **Frequently:** at least twice a week.

Severity:

- **Mild:** heartburn is present but leads to little or no discomfort or distress.
- **Moderate:** heartburn leads to discomfort or is disruptive (for example, you need to take medication to manage it).
- **Severe:** heartburn leads to severe discomfort, distress or is very disruptive (for example, you have trouble doing things or falling asleep).

PLEASE CHECK THAT YOU ANSWERED ALL THE QUESTIONS

CONTINUE TO NEXT PAGE

Modified GIDS-PD – Page 9

GIDS-PD* | THE GASTROINTESTINAL DYSFUNCTION SCALE IN PARKINSON'S DISEASE
*modified

12. Over the past month , have you experienced nausea?

Yes No

If Yes,
Frequency:

- **Occasionally:** less than once a week.
- **Often:** on average, once a week.
- **Frequently:** at least twice a week.

Severity:

- **Mild:** nausea is present but leads to little or no discomfort or distress.
- **Moderate:** nausea leads to discomfort or is disruptive (for example, you need to take anti-sickness medication to manage it or it affects your appetite).
- **Severe:** nausea leads to severe discomfort, distress or is very disruptive (for example, it keeps you from doing things or it makes you vomit).

PLEASE CHECK THAT YOU ANSWERED ALL THE QUESTIONS

CONTINUE TO NEXT PAGE

Modified GIDS-PD – Page 10

08/09

GIDS-PD*| THE GASTROINTESTINAL DYSFUNCTION SCALE IN PARKINSON'S DISEASE
*modified

We would also like to ask you some important questions about your lifestyle that may contribute to your gut health. For each question, please **tick the statement that best describes your lifestyle**. Be sure to read all the statements in each item. Please tick **only one** answer.

OVER THE LAST MONTH:

A. Which diet best represents most of your meals?

- ○ **Western Diet** (rich in meat and roasted potatoes/vegetables)
- ○ **Mediterranean Diet** (rich in meat, fish, fresh vegetables and fresh fruits)
- ○ **Asian Diet** (rich in noodles, rice and cooked vegetables)
- ○ **Indian Diet** (rich in curry, grains and lentils)
- ○ **Vegetarian/Vegan** (excluding meat or animal derived products from meals)
- ○ **Mixed diet** (you do not follow a particular diet pattern, or your diet is a mixture of some of the above)

B. On average, how many glasses of water or non-fizzy juice did you drink per day?

- ○ Less than 1 glass a day (a few per week)
- ○ 1-3 glasses a day
- ○ More than 3 glasses a day

C. How many caffeinated drinks (for example, coffee, tea and energy drinks) did you have per day?

- ○ Less than 1 glass a day (a few per week)
- ○ 1-3 glasses a day
- ○ More than 3 glasses a day

D. How many times did you exercise for more than 30 minutes (for example, fitness classes, brisk walking or cycling for at least 30 minutes)?

- ○ Less than once a week
- ○ 1 to 3 exercise sessions a week
- ○ More than 3 exercise sessions a week

PLEASE CHECK THAT YOU ANSWERED ALL THE QUESTIONS

CONTINUE TO NEXT PAGE ▸

Modified GIDS-PD – Page 11

09/09

GIDS-PD* | THE GASTROINTESTINAL DYSFUNCTION SCALE IN PARKINSON'S DISEASE
*modified

E. What are your smoking habits?

- ○ I have never smoked
- ○ I am an ex-smoker
- ○ I currently smoke (daily or occasionally)

F. Have you EVER been diagnosed with any of the following gastrointestinal disorders by a medical doctor?

DISORDER	YES	NO	IF YES, YEAR OF DIAGNOSIS:	CURRENTLY TAKING MEDICATION FOR IT?	
Constipation	○	○		○ Yes	○ No
Irritable bowel syndrome (IBS)	○	○		○ Yes	○ No
Crohn's Disease	○	○		○ Yes	○ No
Gastroesophageal reflux (also known as Heartburn)	○	○		○ Yes	○ No
Ulcerative Colitis	○	○		○ Yes	○ No
Diverticular Disease	○	○		○ Yes	○ No
Colon Cancer	○	○		○ Yes	○ No
Other: _____	○	○		○ Yes	○ No

THANK YOU FOR YOUR COOPERATION

CONTINUE TO NEXT PAGE ▸

Modified GIDS-PD – Page 12

GIDS-PD* | THE GASTROINTESTINAL DYSFUNCTION SCALE IN PARKINSON'S DISEASE
*modified

SCORING INSTRUCTIONS

Items 1 through 12 are scored as follows:
(except for Item 1-frequency which is inverted)

FREQUENCY	SEVERITY
Occasionally: 1	Mild: 1
Often: 2	Moderate: 2
Frequently: 3	Severe: 3

The GIDS-PD* can be divided into 3 subscores, each constituted by a set of items:

SUBSCORES	ITEMS
Constipation	1, 2, 3 and 4
Bowel Irritability	5, 6, 7 and 8
Upper GI	9, 10, 11 and 12

Items **1a**, **A**, **B**, **C**, **D**, **E** and **F** provide additional information but are **not used for scoring**.
The total score for each item is computed by multiplying frequency and severity scores.

The total score of the GIDS-PD* is computed by adding the total scores of items 1 through 12, resulting in a minimum score of 1 and a maximum score of 108.

ITEM	FREQUENCY SCORE			SEVERITY SCORE			TOTAL ITEM SCORE (F X S)	
1	**3**	**2**	**1**	1	2	3		CONSTIPATION SUBSCORE
2	1	2	3	1	2	3	+	
3	1	2	3	1	2	3	+	
4	1	2	3	1	2	3	+	
5	1	2	3	1	2	3	+	BOWEL IRRITABILITY SUBSCORE
6	1	2	3	1	2	3	+	
7	1	2	3	1	2	3	+	
8	1	2	3	1	2	3	+	
9	1	2	3	1	2	3	+	UPPER GI SUBSCORE
10	1	2	3	1	2	3	+	
11	1	2	3	1	2	3	+	
12	1	2	3	1	2	3	+	
TOTAL GIDS-PD* SCORE							=	

*modified

5 MOCA

Montreal Cognitive Assessment

MoCA tests were alternated to avoid learning effects. The sequence of versions for testing for each participant is listed in the table below:

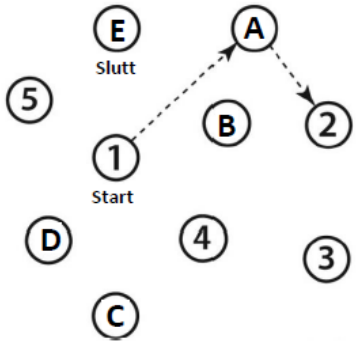
Visit	Version
1 (Week 0)	Version 8.3 Norwegian version
2 (Week 4)	Version v8.1 Norwegian version
3 (Week 8)	Version V8.2 Norwegian version
4 (week 12)	Version v8.3 Norwegian version

MocA – Version 8.1 Norwegian version

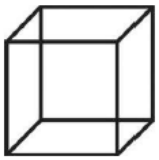
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 8.1 Norwegian version

Navn:
Utdanning (i år): Fødselsdato:
Kjønn: DATO:

VISUOKONSTRUKTIV/EKSEKUTIV — POENG



Kopier kube (1 poeng)



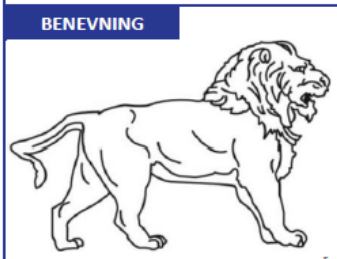
[ ] [ ]

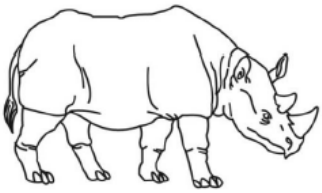
Tegn en klokke (ti over elleve) (3 poeng)

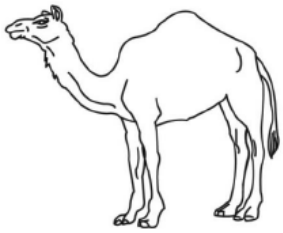
[ ] Kontur [ ] Tall [ ] Visere

__/5

BENEVNING







[ ] [ ] [ ]

__/3

HUKOMMELSE Les ordene, deltageren må gjenta dem. Gjør to forsøk, selv om første forsøk gjennomføres helt riktig. Gjør gjenkalling etter 5 minutter.

	ANSIKT	FLØYEL	KIRKE	TUSENFRYD	RØD
1. forsøk					
2. forsøk					

INGEN POENG

OPPMERKSOMHET Les rekken med tall (1 tall/sekund).
Deltageren skal gjenta dem i forlengs rekkefølge. [ ] 2 1 8 5 4
Deltageren skal gjenta dem i baklengs rekkefølge. [ ] 7 4 2

__/2

Les listen med bokstaver. På hver bokstav A skal deltageren banke på bordet med hånden sin. Ingen poeng ved ≥ 2 feil.
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Begynn fra 100 og trekk fra 7 flere ganger etter hverandre. [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 eller 5 riktige subtraksjoner: 3 poeng, 2 eller 3 riktige: 2 poeng, 1 riktig: 1 poeng, 0 riktig: 0 poeng

__/3

SPRÅK Gjenta: Gjenta etter meg: Det eneste jeg vet, er at Jon er den som skal hjelpe i dag. [ ]
Katten gjemte seg alltid under sofaen når det var hunder i rommet. [ ]

__/2

Ordflyt: Si så mange ord du kan komme på som begynner med F, i løpet av ett minutt. [ ] ____ (N ≥ 11 ord)

__/1

ABSTRAKSJON Likheten mellom for eksempel en banan og en appelsin = frukt [ ] tog- sykkel [ ] klokke - linjal

__/2

UTSATT GJENKALLING

(MIS)	Ord skal gjenkalles UTEN STIKKORD	ANSIKT [ ]	FLØYEL [ ]	KIRKE [ ]	TUSENFRYD [ ]	RØD [ ]	Kun poeng for gjenkalling UTEN STIKKORD
X3							
X2	Kategori-stikkord						
X1	Flere valg som stikkord						MIS = ____ / 15

Hukommelse-indeks-skåre (MIS)

__/5

ORIENTERING [ ] Dato [ ] Måned [ ] År [ ] Ukedag [ ] Sted [ ] By

__/6

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MIS: /15
(Normal ≥ 26/30)
Legg til 1 poeng dersom ≤12 års utdanning

TOTAL SKÅRE __/30

Administrert av: _____

Opplæring og sertifisering er nødvendig for å sikre nøyaktighet.

MOCA - Norway/Norwegian - Version of 31 Oct 2018 - Mapi.
ID061021 / MOCA-8.1-Test_AU1.0_nor-NO.doc

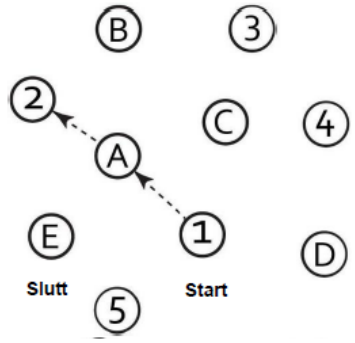
MocA – Version 8.2 Norwegian version

MONTREAL COGNITIVE ASSESSMENT (MOCA®)

Version 8.2 Norwegian (Norway)

Navn:
Utdanning (i år): Fødselsdato:
Kjønn: DATO:

VISUOKONSTRUKTIV/EKSEKUTIV — POENG



Kopier stol

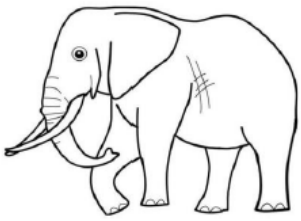
Tegn en klokke (ti over ni) (3 poeng)

[ ] [ ] [ ] Kontur [ ] Tall [ ] Visere

__/5

BENEVNING

[ ]



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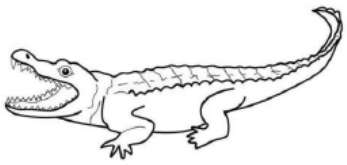

[ ]

__/3

HUKOMMELSE — Les ordene, deltakeren må gjenta dem. Gjør to forsøk, selv om første forsøk gjennomføres helt riktig. GJør gjenkalling etter 5 minutter.

	HÅND	NYLON	PARK	GULROT	ORANSJE
1. forsøk					
2. forsøk					

INGEN POENG

OPPMERKSOMHET — Les rekken med tall (1 tall/sekund)

Deltakeren skal gjenta dem i forlengs rekkefølge. [ ] 8 1 5 2 4

Deltakeren skal gjenta dem i baklengs rekkefølge. [ ] 2 4 7

__/2

Les listen med bokstaver. På hver bokstav A skal deltakeren banke i bordet med hånden sin. Ingen poeng ved ≥ 2 feil.

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Begynn fra 70 og trekk fra 7 flere ganger etter hverandre. [ ] 63 [ ] 56 [ ] 49 [ ] 42 [ ] 35

4 eller 5 riktige subtraksjoner: 3 poeng, 2 eller 3 riktige: 2 poeng, 1 riktig: 1 poeng, 0 riktig: 0 poeng

__/3

SPRÅK — Gjenta: Tyven av den grå bilen ble stoppet av politiet. [ ]

Eleven dro tilbake til skolen uten sine bøker og blyanter. [ ]

__/2

Ordflyt: Si så mange ord du kan komme på som begynner med S, i løpet av ett minutt. [ ] ____ (N ≥ 11 ord)

__/1

ABSTRAKSJON — Likheten mellom for eksempel en banan og en appelsin = frukt [ ] seng - bord [ ] brev - telefon

__/2

UTSATT GJENKALLING — Hukommelse-indeks-skåre (MIS)

(MIS)	Ord skal gjenkalles UTEN STIKKORD	HÅND	NYLON	PARK	GULROT	ORANSJE	Kun poeng for gjenkalling UTEN STIKKORD
X3		[ ]	[ ]	[ ]	[ ]	[ ]	
X2	Kategori-stikkord						
X1	Flere valg som stikkord						MIS = ____ / 15

__/5

ORIENTERING [ ] Dato [ ] Måned [ ] År [ ] Ukedag [ ] Sted [ ] By

__/6

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Administrert av: _____

Opplæring og sertifisering er nødvendig for å sikre nøyaktighet.

MIS: /15 (Normal ≥ 26/30)

Legg til 1 poeng dersom ≤ 12 års utdanning

TOTAL SKÅRE __/30

MOCA - Norway/Norwegian
Translated by: Siri Weider (May 24, 2022)

MocA – Version 8.3 Norwegian version

MONTREAL COGNITIVE ASSESSMENT (MOCA®)

Version 8.3 Norwegian (Norway)

Navn:
Utdanning (i år): Fødselsdato:
Kjønn: DATO:

VISUOKONSTRUKTIV/EKSEKUTIV — POENG

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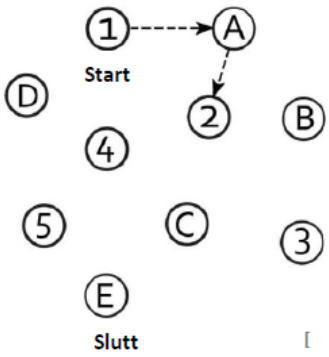
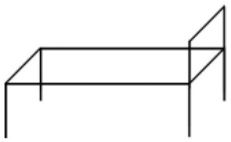




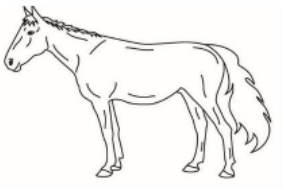
[ ] [ ]

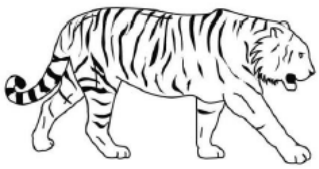
Tegn en klokke (fem over ti)
(3 poeng)

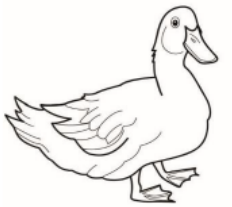
[ ] Kontur [ ] Tall [ ] Visere

__/5

BENEVNING







[ ] [ ] [ ]

__/3

HUKOMMELSE — Les ordene, deltakeren må gjenta dem. Gjør to forsøk, selv om første forsøk gjennomføres helt riktig. Gjør gjenkalling etter 5 minutter.

	FOT	BOMULL	SKOLE	TOMAT	HVIT
1. forsøk					
2. forsøk					

INGEN POENG

OPPMERKSOMHET — Les rekken med tall (1 tall/sekund)

Deltakeren skal gjenta dem i forlengs rekkefølge. [ ] 2 4 8 1 5

Deltakeren skal gjenta dem i baklengs rekkefølge. [ ] 4 2 7

__/2

Les listen med bokstaver. På hver bokstav A skal deltakeren banke i bordet med hånden sin. Ingen poeng ved ≥ 2 feil.

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Begynn fra 60 og trekk fra 7 flere ganger etter hverandre. [ ] 53 [ ] 46 [ ] 39 [ ] 32 [ ] 25

4 eller 5 riktige subtraksjoner: 3 poeng, 2 eller 3 riktige: 2 poeng, 1 riktig: 1 poeng, 0 riktig: 0 poeng

__/3

SPRÅK — Gjenta: Barnet gikk tur med hunden sin i parken etter midtnatt. [ ]

Kunstneren var ferdig med maleriet sitt i riktig tid til utstillingen. [ ]

__/2

Ordflyt: Si så mange ord du kan komme på som begynner med B, i løpet av ett minutt.. [ ] ____ (N ≥ 11 ord)

__/1

ABSTRAKSJON — Likheten mellom for eksempel en banan og en appelsin = frukt [ ] hammer - skruetrekker [ ] fyrstikk - lampe

__/2

UTSATT GJENKALLING

Hukommelse-indeks-skåre (MIS)

(MIS)	Ord skal gjenkalles UTEN STIKKORD	FOT [ ]	BOMULL [ ]	SKOLE [ ]	TOMAT [ ]	HVIT [ ]	Kun poeng for gjenkalling UTEN STIKKORD
X3							
X2	Kategori-stikkord						
X1	Flere valg som stikkord						MIS = ____ / 15

__/5

ORIENTERING [ ] Dato [ ] Måned [ ] År [ ] Ukedag [ ] Sted [ ] By

__/6

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Administrert av: _____

Opplæring og sertifisering er nødvendig for å sikre nøyaktighet.

MIS: /15
(Normal ≥ 26/30)
Legg til 1 poeng dersom ≤ 12 års utdanning

TOTAL SKÅRE __/30

MOCA - Norway/Norwegian
Translated by: Siri Weider (May 24, 2022)

6 EQ-5D-EL

The 5-level EQ-5D

EQ-5D-5L – Page 1

Spørreskjema om helse

Norsk versjon, for Norge

(Norwegian version for Norway)

EQ-5D-5L – Page 2

Under hver overskrift ber vi deg krysse av den ENE boksen som best beskriver helsen din I DAG.

GANGE

- Jeg har ingen problemer med å gå omkring ❑
- Jeg har litt problemer med å gå omkring ❑
- Jeg har middels store problemer med å gå omkring ❑
- Jeg har store problemer med å gå omkring ❑
- Jeg er ute av stand til å gå omkring ❑

PERSONLIG STELL

- Jeg har ingen problemer med å vaske meg eller kle meg ❑
- Jeg har litt problemer med å vaske meg eller kle meg ❑
- Jeg har middels store problemer med å vaske meg eller kle meg ❑
- Jeg har store problemer med å vaske meg eller kle meg ❑
- Jeg er ute av stand til å vaske meg eller kle meg ❑

VANLIGE GJØREMÅL *(f.eks. arbeid, studier, husarbeid, familie- eller fritidsaktiviteter)*

- Jeg har ingen problemer med å utføre mine vanlige gjøremål ❑
- Jeg har litt problemer med å utføre mine vanlige gjøremål ❑
- Jeg har middels store problemer med å utføre mine vanlige gjøremål ❑
- Jeg har store problemer med å utføre mine vanlige gjøremål ❑
- Jeg er ute av stand til å utføre mine vanlige gjøremål ❑

SMERTER / UBEHAG

- Jeg har verken smerter eller ubehag ❑
- Jeg har litt smerter eller ubehag ❑
- Jeg har middels sterke smerter eller ubehag ❑
- Jeg har sterke smerter eller ubehag ❑
- Jeg har svært sterke smerter eller ubehag ❑

ANGST / DEPRESJON

- Jeg er verken engstelig eller deprimert ❑
- Jeg er litt engstelig eller deprimert ❑
- Jeg er middels engstelig eller deprimert ❑
- Jeg er svært engstelig eller deprimert ❑
- Jeg er ekstremt engstelig eller deprimert ❑

2

EQ-5D-5L – Page 3

- Vi vil gjerne vite hvor god eller dårlig helsen din er I DAG.
- Denne skalaen er nummerert fra 0 til 100.
- 100 betyr den beste helsen du kan tenke deg.
  0 betyr den dårligste helsen du kan tenke deg.
- Sett en X på skalaen for å angi hvordan helsen din er I DAG.
- Skriv deretter tallet du merket av på skalaen inn i boksen nedenfor.

HELSEN DIN I DAG = ☐