ALTHEA
the italian vALidation of THe unifiEd dyskinesiA rating scale

CLINICAL TRIAL PROTOCOL

PROTOCOL SYNOPSIS

TITLE: The Italian vALidation of THe UnifiEd DyskinesiA Rating Scale -The ALTHEA trial

STUDY OBJECTIVE(S)	Phase II: To test the appropriateness of the Italian translation and clear understanding of potentially cultural-sensitive items. To refine the translation, if necessary, prior to validation testing. Phase III: the primary outcome of phase III is to confirm factorial analysis of the Italian version against the factor structure of the English version, by each section of the scale. To be designated as official Italian translation, the comparative fit index (CFI) of the final model for each section of UDysRS has to be ≥ 0.9 relative to the English version.
STUDY DESIGN	The present study is designed as a two-phase prospective, multicentre, methodological, trial. About 10 PD patients with mild, moderate and severe dyskinesias in the coordinator's site will participate in the phase II Cognitive pre-testing. For the large-scale validation testing, 250 PD patients will be included in 10 Italian neurological centres.
STUDY POPULATION	Main selection criteria: 1. Written and signed informed consent; 2. native Italian-speaking patients of either sex; 3. patients suffering from Parkinson's disease ranging from moderate to severe, based on clinical judgement, with dyskinesia 4. presence of a native Italian-speaking caregiver. Main exclusion criteria Patients suffering from Parkinson's disease without dyskinesia
Total expected number of patients: Expected number of sites:	10 patients in phase II 250 patients in phase III 1 in phase II 10 in phase III

STATISTICAL CONSIDERATIONS	**Sample size calculation:** The requested sample size of 250 PD patients has been calculated on the need for 7 to 10 subjects to be assessed per item of the questionnaire in order to perform the statistical tasks needed to validate the instrument. There are 26 items on the UDysRS. **Statistical methods:** The primary outcome for designation for approval of the Italian version will be a confirmatory factor analysis run against the established English version factor structure by each section. To be designated as official translation the comparative fit index (CFI) of the final model for each section of the UDysRS must be ≥ 0.9 relative to the English version. The factor analysis will be performed by the MDS statisticians.
DURATION OF STUDY PERIOD	**Start date:** (first patient in): April 2013 **End date:** (last patient in): October 2013 Max duration for a given patient: single session
SUBSTUDY	An ancillary substudy will be conducted in patients who will accept to undergo additional testing. Aim of the substudy is to test presence of impulsive-compulsive traits in PD patients using QUIP-RS. as well as depressive symptoms using the BECK II -BDI 21 items.

1. LIST OF ABBREVIATIONS

ANCOVA: Analysis of Covariance.
CFI: Comparative fit index
CRA: Clinical Research Associate
CRF: Case Report Form.
CSR: Clinical Study Report.
CT: Computed Tomography.
CV: Curriculum Vitae.
DIF: Differential item function
GCP: Good Clinical Practice.
IRB/IEC: Institutional Review Board/Independent Ethics Committee.
IVRS: Interactive Voice Response System. .
m: month.
MRI: Magnetic Resonance Imaging.
MDS: Movement Disorders' Society
n: number.
PD: Parkinson's Disease
PD-CRS: Parkinson's Disease-Cognitive Rating Scale
PP: Per-Protocol.
PT: Preferred Term.
SAP: Statistical Analysis Plan.
SD: Standard Deviation.
SOP: Standard Operating Procedure.
UDysRS: Unified Dyskinesia Rating Scale
WOC: Withdrawal of Consent.

2. INTRODUCTION AND RATIONALE

In 1998, an international symposium specifically devoted to dyskinesia in PD was held in Toulouse, France, and its summary document emphasized the critical need for a single validated scale for assessing dyskinesia.
Because of the impact of dyskinesia on activities of daily living, quality of life, and consequent global disability of patients with advanced PD, the Movement Disorder Society (MDS) organized a systematic review of the clinimetric properties of the scales used to measure dyskinesia in PD's patients. Eight rating scales for dyskinesia in PD were identified. They were: the Abnormal Involuntary Movement Scale (AIMS), the UPDRS part IV, with its recent revision by the MDS, the Obeso Dyskinesia Rating Scale, the Rush Dyskinesia Rating Scale, the Clinical Dyskinesia Rating Scale,1 the Lang-Fahn Activities of Daily Living Dyskinesia Scale, the Parkinson Disease Dyskinesia Scale (PDYS-26), and the Unified Dyskinesia Rating Scale (UDysRS). Based on this review, two of the reviewed dyskinesia scales (AIMS and the Rush Dyskinesia Rating Scale) fulfilled pre-defined criteria for Recommended for use in PD populations.

The Unified Dyskinesia Rating Scale (UDysRS) is a new rating scale developed specifically for the assessment of dyskinesia in PD. The UDysRS contains both self-evaluation questions (by the patient alone or with their caregivers) and items that are assessed directly by the physician to objectively rate the abnormal movements associated with PD.
The UDysRS consists of two primary sections (Historical and Objective); each section is divided in two parts. All parts consist of several items, and each item is scored on a scale from 0 to 4 in a Likert model (0, normal; 4, severe). The total score of the UDysR ranges from 0 to 104.
The UDysRS represents a comprehensive rating tool that captures patient perceptions, time factor of dyskinesia, anatomical distribution, phenomenology (dystonia vs. other dyskinesia), objective impairment, and severity and disability of dyskinesia and dystonia in PD. The tested clinimetric properties of the scale range are excellent. The scale has not been evaluated for responsiveness testing to an intervention and has not been used by other groups beside the researchers involved in its development.
The Unified Dyskinesia Rating Scale (UDysRS) is owned by the Movement Disorder Society and has been developed with clinimetric validation in its original English version.
As the MDS is an international society, a MDS-UDysRS translation program for non-English official versions was recently launched.
The present study is part of this international program and deals with the translation and validation program for the Italian version of the MDS UDysRS.

The program will be articulated in three steps:

- Phase I: translation and back-translation of the MDS-UDysRS in Italian (completed)
- Phase II: Cognitive pre-testing. This step is aimed at a preliminary testing of a subset of potentially culturally sensitive items in a limited set of PD patients (approximately ....). Should this phase identify issues in the understanding and ease of use of some items a revised translation of some individual items might be envisaged.
- Phase III: large validation testing: this phase will involve 250 PD patients from 10 Italian PD centres.

The ALTHEA protocol deals with phase II and III of the program.

An ancillary substudy will be conducted in patients who will accept to undergo additional cognitive testing. Aim of the substudy is to test the presence of impulsive-compulsive traits in PD patients using the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS), as well as of depressive symptoms using the BECK II -BDI 21 items

3. STUDY OBJECTIVES

3.1. Phase II

To test the appropriateness of the Italian translation and clear understanding of potentially cultural-sensitive items. To refine the translation, if necessary, prior to validation testing.

3.2. Phase III

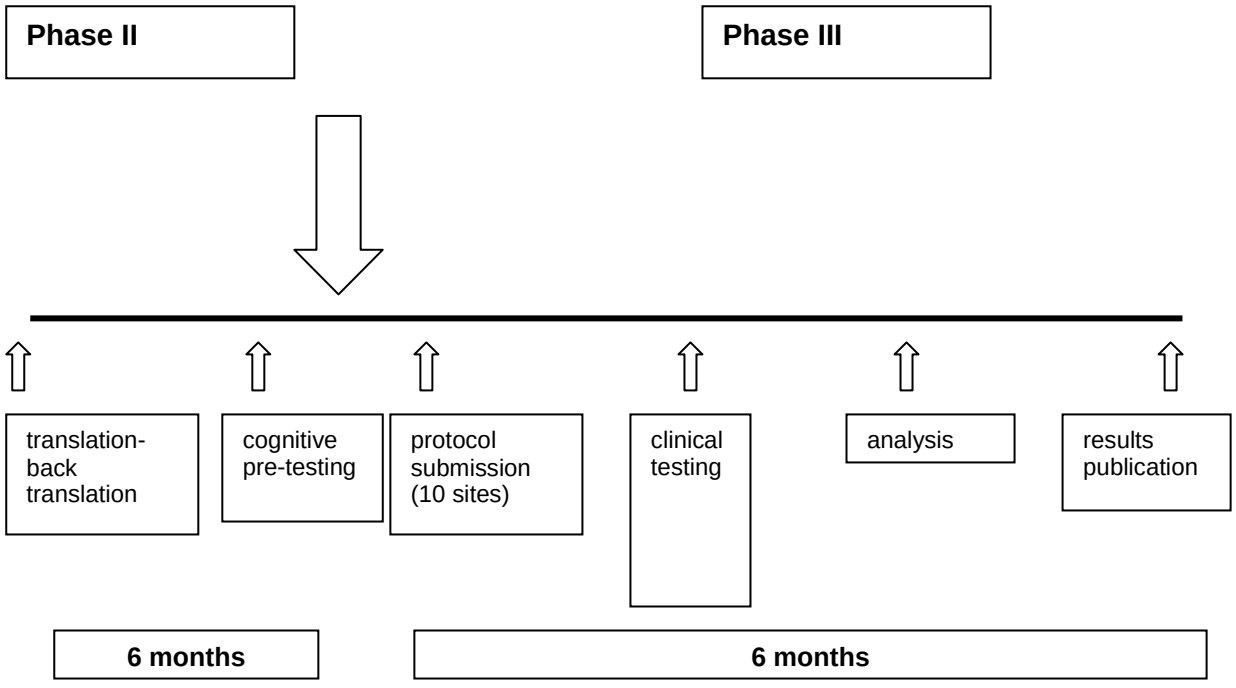
The primary outcome of phase III is to confirm factorial analysis of the Italian version against the factor structure of the English version, by each of the four sections of the scale. To be designated as official Italian translation, the Comparative fit index (CFI) of the final model for each section of UDysRS has to be ≥ 0.9 relative to the English version.

4. STUDY DESIGN

4.1. Description of the Protocol

The present study is designed as a two-phase prospective, multicentre methodological trial.
About 10 PD patients will participate in the phase II Cognitive testing.
For the large-scale validation testing, 250 PD patients will be included in 10 Italian neurological centres. The number is based on the need for 7 to 10 subjects to be assessed per item of the questionnaire in order to perform the statistical tasks needed to validate the instrument.

Study scheme:



4.2. Duration of study participation

Each PD patient will undergo a single administration of the UDysRS scale during a clinic visit.

4.3. Interim analysis

No interim analysis is planned.

4.4. Study committees

The MDS Steering Committee is in charge of coordinating the activities of local translation programs, providing the factor analysis scores and to approve the different steps of the validation process such as: approval of the provisional translation for the cognitive testing and for the validation testing as well as revising and performing the statistical analysis.

The Italian Coordination Team is represented by Prof. Giovanni Abruzzese, Dr. Angelo Antonini and Prof. Paolo Barone, who will be in charge of finalising the local protocol, identifying participating centres, supervising the conduct of the program, propose local ancillary programs and define publication policy.

5. SELECTION OF PATIENTS

5.1. Number of patients planned

For phase II, approximately 10 PD patients will be tested in one site.
For phase III a total of around 250 native Italian-speaking PD patients will be recruited in 10 Neurological centres, specialists in movement disorders. Each centre is requested to commit to enrol between 20 and 40 subjects (25 as an average).

5.2. Inclusion criteria

1. Written and signed informed consent;
2. native Italian-speaking patients or either sex;
3. patients suffering from Parkinson's disease ranging from mild to severe, based on clinical judgement with dyskinesia;
4. presence of a native Italian-speaking caregiver.

Patients should be selected as to include all different categories of PD in terms of disease severity and good balance in gender. A central minimization procedure will be adopted in order to achieve good balance.

5.3. Exclusion criteria

Patients suffering from Parkinson's disease without dyskinesia.

6. ASSESSMENTS

6.1. Parkinson's Disease characteristics

The following information will be collected:

- disease history: age at onset, initial symptoms;
- disease severity;
- drug treatment for PD;
- presence of motor fluctuations and ON state at the time of the examination
- presence and type of dyskinesias

Age, gender and education level will also be recorded.

6.2. Italian version of the UDysRS

6.2.1. First version of the Italian translation of the UDysRS

Local translation and back translation have already been completed as per the MDS non-English translation program. Selected items from this provisionally approved translation will be incorporated in a specific guide and used for the cognitive pre-testing phase of the program .
After revision and approval by the Clinimetric Steering Committee (CSC) the local version will be designated WORKING DRAFT and undergo clinimetric testing.

6.3. Clinical assessment methods

Native Italian speaking neurologists, specialised in movement disorders will qualify to perform the ratings.
Prior to starting the clinical validation phase, all trialists will participate in a training sessions leaded by the Italian Coordination Team and aimed at standardising the assessment methods. No formal inter-rater reliability session will be run.
UDysRS administration will be standardised by adopting as much as possible the following conventions:

- each individual rater should assess a minimum of 5 PD patients and each participating site should contribute a minimum of 20 cases;
- candidate patients should be pre-identified from the PD population already attending the clinic; .
- the patient sample should include samples from different ages, genders, severities of PD and educational levels.
- PD patients with dyskinesia of any grade should be selected; presence of a native Italian-speaking caregiver will be mandatory; the caregiver should be close enough to the patient as to provide reliable information.
- testing should be organised in a quiet room with no external interference (portable should be switched off); patients must be assessed while in “on” phase;
- there should be no missing answers in the patients questionnaire.

Administration of the whole scale should take 30-40 minutes: time required to complete the scale will be recorded.
Patient’s questionnaire (part 1B and 2B) will be handled to the patient and to the caregiver and then revised by the rater. Part 1A and 2A will be administered by the rater as an interview.
Results of part 3 and part 4 examinations will be directly recorded in the UDysRS form which will constitute the source documents.
The original forms will be collected for data entry and a copy retained by the centre.

7. STUDY PROCEDURES

7.1. Phase II

Selected items of the provisional Italian translation of the patient questionnaire will be incorporated in a specific guide and administered to 10 PD patients overall.

7.1.1. *Cognitive* pre-*testing*

PD patients with dyskinesia fulfilling inclusion/exclusion criteria will be invited to take part in this phase and will be asked to sign a written informed consent.
The patient will then complete the questionnaire with the help of the caregiver. Answers will be revised by the rater.
Questions will be asked to the patient as well as to the examiner after each item to assess patient and examiner understanding and ease of comprehension for instructions and response options.
Completed forms will be collected and results assessed by the CSC. Based on this review, revision of the translation will be requested or the provisional version approved for the clinimetric testing phase.

7.2. Phase III

This phase will involve all participating sites and will start after completion of phase II and once the local EC approval for each site has been obtained.

7.2.1. Validation testing

PD patients with dyskinesia fulfilling inclusion/exclusion criteria will be invited to take part in this phase and will be asked to sign a written informed consent.

After revision of the clinical status of the patient, the examiner will administer parts 1B and 2B and let the patient complete the patient's questionnaire.

Part 3 and 4 will then be rated. Results will be recorded in the specific form (CRF) produced for the study. As foreseen by the rating scale, assessment of part 3 and 4 may be recorded. Registrations of these evaluations will be retained only for those patients giving specific consent in writing.

Information related to disease history and severity, drug treatment, age and gender , presence of motor fluctuations and ON/OFF state at the time of the examination will also be captured in the CRF. Education level will be recorded.

Each participating site should complete rating of 20 to 40 PD patients within a maximum of 4 months (5-10 patients/month).
Completed CRFs will be sent by courier to the CRO which will be in charge of data entry in a specific web-based data base set up by MDS.

7.2.2. Definition of source data

The CRF will be considered as source documentation for the following items:

- UDysRS scoring
- duration of the administration
- education level

All other information that are reported in the CRF must be supported by source documentation; in particular hospital records should report documentation as to disease history, PD treatment, medical history.

8. STATISTICAL CONSIDERATIONS

8.1. Statistical and analytical plans

The primary outcome for designation for approval of the Italian version will be a confirmatory factor analysis run against the established English version factor structure by each section. To be designated as official translation the comparative fit index (CFI) of the final model for each section of the UDysRS must be ≥ 0.9 relative to the English version. The factor analysis scores will be provided by the MDS statisticians.

8.2. Determination of sample size

The requested sample size of 250 PD patients has been calculated on the need for 7 to 10 subjects to be assessed per item of the questionnaire in order to perform the statistical tasks needed to validate the instrument (26 items on the UDysRS).

8.3. Study patient description

Patients demographics will be described as means, standard deviations and ranges, median and interquartile interval for non gaussian distributed variable as for quantitative variables. Absolute and relative frequencies will be provided for qualitative variables. 95% Confidence intervals will be provided if the case.
Description of PD characteristics will include age at onset, duration of PD, severity, type of therapy. In addition presence of motor fluctuations and ON/OFF state at the time of the examination will be described as means and percentages.

8.4. General statistical approach

All summary tables for quantitative parameters will display mean, standard deviation, median and range (minimum and maximum). Categorical data will be summarized using counts and percentages. Missing data will not be categorized in the summaries and will not be taken into account in the denominator. No missing data are expected for the UDysRS items.

8.5. Primary endpoint

Analysis of primary endpoint will be performed by the mean of a confirmatory factor analysis run against the English version factor structure by each section. This analysis will be performed by the MDS statistician.

9. ETHICAL AND REGULATORY STANDARDS

9.1. Ethical principles

This Clinical Trial will be conducted in accordance with the principles laid down by the18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for Good Clinical Practice.

9.2. Laws and regulations

This Clinical Trial will be conducted in compliance with all international laws and regulations, and Italian laws and regulations, as well as any applicable guidelines.

9.3. Informed consent

The Investigator should fully inform the Patient of all pertinent aspects of the study including the written information given approval/favourable opinion by the Ethics Committee (EC).
Prior to a patient's participation in the Trial, the written Informed Consent Form (ICF) should be signed; name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

9.4. Ethics Committee (EC)

The Investigator must obtain approval of this Protocol and of the ICF by the appropriate Ethics Committee, and is required to forward to the Sponsor a copy of the written and dated approval/favourable opinion signed by the Chairman, with Ethics Committee composition.
The Protocol title and version number, the documents reviewed (Clinical Trial Protocol, Informed Consent Form, Investigator's CV, etc.) and the date of the review should be clearly stated on the written EC approval/favourable opinion.

During the Clinical Trial, any amendment or modification to the Protocol should be submitted to the Ethics Committee. If requested, a progress report is sent to the Ethics Committee and a summary of the study results at the end of the Trial.

10. RESPONSIBILITIES

10.1. Responsibilities of the Investigator(s)

The Investigator(s) undertake(s) to perform the study in accordance with this Clinical Trial Protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.
The Investigator is required to ensure compliance with all procedures required by the Protocol and by study procedures provided by the Sponsor. The Investigator agrees to provide reliable data and all information requested by the Protocol (with the help of the Case Report Form (CRF) and to ensure direct access to source documents to Sponsor representatives.

10.2. Responsibilities of the Sponsor

The Sponsor of this study is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Protocol as regards ethics, Protocol compliance, integrity and validity of the data recorded on the Case Report Forms. To this purpose all participating Investigators will attend a pre-study meeting during which extensive training to the protocol and study procedures will be given by the Italian Coordination Team.

10.3. Use and completion of Case Report Forms (CRFs) and additional request

It is the responsibility of the Investigator to maintain adequate and accurate CRFs designed by the Sponsor/CRO to record data pertinent to the clinical investigation.
All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.
Should a correction be made, the information to be modified must not be overwritten. The corrected information will be transcribed by the authorized person next to the previous value, initialed and dated.
The computerized handling of the data by the CRO after receipt of the CRFs may generate additional requests (queries) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be appended to the CRFs held by the Investigator and the CRO.

11. ADMINISTRATIVE RULES

11.1. Curriculum Vitae

An updated copy of the curriculum vitae limited to the experience, qualification and training for each Investigator will be provided to the CRO prior to the beginning of the study.

11.2. Record retention in study sites (s)

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents. It is recommended that the Investigator retain the study documents at least seven (7) years after the completion of the study.

12. CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the study, including, but not limited to the Protocol, the CRFs and the results obtained during the course of the study, is confidential. The Investigator or any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.
However, the submission of this Clinical Trial Protocol and other necessary documentation to the Ethics Committee is expressly permitted, the EC members having the same obligation of confidentiality.

13. DATA PROTECTION

The patient's personal data and Investigator's personal data which may be included in the Sponsor database shall be treated in compliance with all applicable laws and regulations.
When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor/CRO shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

14. PUBLICATIONS AND COMMUNICATIONS

MDS Steering Committee will be in charge of drafting the main study results on behalf of the Italian Investigators. All participating sites will be acknowledged in the final publication. Ancillary publications will be revised and approved by the Italian Coordination Team.

15. BIBLIOGRAPHIC REFERENCES

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2. Goetz CG, Nutt JG, Stebbins GT. The unified dyskinesias rating scale: presentation and clinimetric profile. Mov Disord 2008;23:2398–2403
3. C.G. Goetz et al: Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Testing Results. Movement Disorders Vol. 23, No 15, 2008, pp. 2129-2170

Appendix 1

SUBSTUDY

Aim of the substudy is to perform an ancillary evalution of behavioural aspects of patients with Parkinson's disease and dyskinesia, with particular reference to the presence of impulsive-compulsive traits by means of the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS) [1] and of depressive symprtoms, as assessed by the patient himself using the BECK II -BDI 21 items[2].
The Montreal Cognitive Assessment (MOCA)[4] test will be adopted as screening tool for possible presence of cognitive impairment.
In addition, the MDS-UPDRS[3] will be administered in order to have a parallel assessment of the severity of PD.

METHODS

After completion of the UDysRS, patients will be administered the MOCA, the MDS-UPDRS, the BECK II and the QUIP-RS. A specific manual with detailed instructions on tests administration will be provided.

Results will be recorded in a scoring sheet and collected for analysis. A detailed statistical analysis plan will be developed prior to the analysis.

REFERENCES

1. Weintraub D, Mamikonyan E, Papay K, Shea JA, Xie SX, Siderowf A.: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale. Mov Disord. 2012 Feb;27(2):242-7. doi: 10.1002/mds.24023. Epub 2011 Dec 1

2. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961 June;4:561-71.

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4. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment (MoCA): A brief screening tool for mild cognitive impairment. J Am Geriatr. Soc. 53:695-699, 2005