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ORIGINAL ARTICLE

Adherence to anti-Parkinson drug therapy in the "REASON" sample of Italian patients with Parkinson's disease: the linguistic validation of the Italian version of the "Morisky Medical Adherence scale-8 items"

G. Fabbrini · G. Abbruzzese · P. Barone · A. Antonini · M. Tinazzi · G. Castegnaro · S. Rizzoli · D. E. Morisky · P. Lessi · R. Ceravolo · On behalf of the REASON study group

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Abstract Information about patients' adherence to therapy represents a primary issue in Parkinson's disease (PD) management. To perform the linguistic validation of the Italian version of the self-rated 8-Item Morisky Medical Adherence Scale (MMAS-8) and to describe in a sample of Italian patients affected by PD the adherence to anti-Parkinson drug therapy and the association between adherence and some socio-demographic and clinical features. MMAS-8 was translated into Italian language by two independent Italian mother-tongue translators. The consensus version was then back-translated by an English mother-tongue translator. This translation process was followed by a consensus meeting between the authors of translation and investigators and then by two comprehension tests. The translated version of the MMAS-8 scale was then administered at the baseline visit of the "REASON" study (Italian Study on the Therapy Management in Parkinson's disease: Motor, Non-Motor, Adherence and Quality Of Life Factors) in a large sample of PD patients. The final version of the MMAS-8 was easily understood. Mean ± SD MMAS-8 score was 6.1 ± 1.2. There were no differences in adherence to therapy in relationship to disease severity, gender, educational level or decision to change therapy. The Italian version of MMAS-8, the key tool of the REASON study to assess the adherence to therapy, has shown to be understandable to patients with PD. Patients enrolled in the REASON study showed medium therapy adherence.

Keywords Adherence · Parkinson's disease · Validation · Comprehension

Abbreviations

APD	Anti-Parkinson drug
HY	Hoehn and Yahr

The members of the REASON study group are listed in "Appendix".

G. Fabbrini
Sapienza University of Rome and IRCCS Neuromed Institute, Pozzilli (IS), Italy

G. Abbruzzese
Neurosciences, Ophthalmology and Genetics Department, University of Genova, Genoa, Italy

P. Barone
Schola Medica Salernitana, University of Salerno, Salerno, Italy

A. Antonini
Department for Parkinson's Disease, IRCCS San Camillo, Venice, Italy

M. Tinazzi
Department of Neurological, Neuropsychological, Morphological and Movement Sciences, University of Verona, Verona, Italy

G. Castegnaro · S. Rizzoli
Medidata, Studi e Ricerche, Modena, Italy

D. E. Morisky
Department of Community Health Sciences, UCLA Fielding School of Public Health, Los Angeles, CA, USA

P. Lessi
Boehringer-Ingelheim Italia S.p.A, Medical Clinical Operation, Milan, Italy

R. Ceravolo (✉)
Neurosciences Department, University of Pisa, Pisa, Italy
e-mail: roberto.ceravolo@med.unipi.it

MMAS-4 4-Item Morisky Medical Adherence Scale
MMAS-8 8-Item Morisky Medical Adherence Scale
PD Parkinson's disease

Introduction

Poor compliance has been recognized as an important issue in several chronic disorders and also in Parkinson's disease (PD) [1]. In PD, low adherence to therapy may be associated with unsatisfactory control of motor symptoms, more time spent in the "off" condition during the day, and worse quality of life [2]. Studies have also shown that poor compliance is more common in younger patients; it is directly correlated with the complexity of drug regimen, with the presence of depression [3], and with cognitive impairment [4]. Improving our knowledge about the adherence to therapy is therefore of primary importance for the correct clinical management of PD patients.

Compliance may be assessed directly by measuring drug levels in body fluids, or indirectly through different approaches such as tablets counts, self-report questionnaires, and epidemiological surveys [2, 3]. Electronic monitoring has also been used in experimental settings [5, 6]. In everyday clinical practice it would be useful to have a simple, reliable questionnaire to assess the adherence to therapy in PD. The Morisky, Green and Levine Medical Adherence Scale is a fast, simple, 4-item, self-assessment questionnaire that has been validated in its psychometric properties and has been widely used to measure adherence to therapy in several therapeutic areas [7, 8]. Elm and collaborators [9] showed the usefulness of the MMAS-4 questionnaire in de novo PD patients included in two clinical trials. In this study, adherence to therapy as measured by the MMAS-4 correlated moderately (Spearman's correlation coefficient 0.38) with objective pill count. Recently, Valldeoriola [4] showed that patient's adherence to therapy as measured by the Morisky, Green, Levine test was lower than that estimated by physicians' subjective perception. To obviate some limitations of the MMAS-4, the questionnaire has been updated with the addition of four further items [10]. Each question of the 8-Item Morisky Medical Adherence Scale (MMAS-8) evaluates patients' behaviours in therapy consumption. The first 7 items have dichotomous responses (0 = Yes; 1 = No) and the last one includes a 5-point Likert scale response. The MMAS-8 showed a higher reliability than the MMAS-4 (Cronbach's $\alpha = 0.83$ vs Cronbach's $\alpha = 0.61$) [10, 11].

As there are currently no validated clinical scales in the Italian language to study the adherence to therapy in PD patients, in the current study we first conducted the linguistic validation of the Italian version of the MMAS-8 according to standardized procedures. The adherence to therapy was then assessed in a large sample of PD patients participating in the REASON study (Italian Study on the Therapy Management in Parkinson's Disease: Motor, Non-Motor, Adherence and Quality Of Life Factors) through the neurologist's subjective evaluation and with the Italian version of the MMAS-8. The association between adherence to therapy and some socio-demographic, clinical and therapeutic variables was assessed too.

Methods

Linguistic validation of the MMAS-8

The translation of the MMAS-8 in Italian was done according to a stepwise process [12] as follows: (a) the translation from the English original version into Italian was carried out in parallel by two independent professional translators, Italian native speakers with English as their first foreign language; (b) the two Italian versions were compared and discussed in a first consensus meeting between the two translators and the research group of the REASON study to reach a consensus version; (c) the back translation of the Italian consensus version into English was carried out by a native English-speaking translator, with Italian as his first foreign language. The English native speaker was purposely kept unaware of the intent and concepts lying behind the material he had been given; (d) in the second consensus meeting between the native English-speaking translator and the research group, the English original version was compared to the back-translated one and possible differences were debated, thus resulting in the revision and change of the first Italian consensus version; (e) the construct validity of each item was evaluated by the developer with the original assessment procedures for the English version, confirming the conceptual content of the backwards translation; (f) a comprehension test for the new consensus version was carried out in order to assess if the questionnaire was easy to understand. The questionnaire was tested in 30 PD patients recruited from six Italian movement disorders centres headed by the REASON study Steering Committee members. Information about comprehension of items and answer mode were collected. Test findings led to the writing of a second Italian version, which was tested and validated on 19 additional PD patients; (g) the final Italian version of the MMAS-8 was eventually produced.

Evaluation of adherence to therapy

REASON is a prospective observational cohort study involving 30 movement disorders centres across Italy.

Patients aged ≥18 years, with a diagnosis of idiopathic PD [13], with a stable anti-parkinsonian treatment in the 3 months prior to baseline, and able to understand and fill out the study questionnaires were recruited from November 2010 until July 2011. A balanced sample of early [Hoehn and Yahr (HY) staging between 1 and 2] and advanced (HY staging between 2.5 and 4) PD patients was enrolled. Patients included in other clinical trials or treated with deep brain stimulation at baseline or who received any infusion therapy (apomorphine and levodopa) in the 12 months prior to baseline were excluded. Given the observational nature of the study, patients were treated only on the basis of the neurologist's decisions, and no randomization procedure was applied. The REASON study required visits at baseline and follow-up at 3, 6 and 9 months afterward [14]. In this paper, we present the data collected at baseline. The study was approved by the local Ethics Committees and signed written informed consent was obtained from each participant. The Steering Committee of the study "Appendix" designed the study and defined methods for data collection.

A neurologist experienced in movement disorders examined patients at each site and filled in the study questionnaire in order to collect socio-demographic data (age, gender, marital, educational and employment status), medical history (general and specific for PD), drug therapy, and his opinion about the need for therapy change. Disease severity was measured according to the modified HY scale, symptoms severity was assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) and general cognitive status with the Mini Mental State Examination (MMSE). Missing responses to MMSE items were considered equal to 0 [15]; completed MMSE forms were considered evaluable for statistical analysis and age- and education-adjusted score was calculated [16, 17].

The neurologist recorded their best guess about patients' adherence to ongoing drug therapy for PD by means of four questions with dichotomous (yes/no) answers about patient compliance to anti-Parkinson therapy, adherence to scheduled time of drug administration, drug abuse and role of caregiver in therapy adherence. The adherence to therapy was also assessed by the Italian version of the MMAS-8 (Fig. 1). Patients with at least six out of eight MMAS-8 answered questions were considered eligible for analyses. For patients with one or two missing responses, missing items were substituted with the sample median value of no missing responses at the same item. The MMAS-8 total score is obtained summing the 8 items and ranges between 0 (lowest adherence) and 8 (highest adherence). According to the MMAS-8 scale, a score <6 defines low adherence, a score between 6 and <8 medium adherence and a score = 8 high adherence [10].

Statistical analyses

Absolute and relative frequencies were calculated for qualitative data; continuous normally distributed variables were expressed as mean ± SD and comparisons between groups were performed by parametric Student's t test and analysis of variance. Differences between categorical variables were tested by χ^2 test. The significance threshold was set to 0.002 (alpha with Bonferroni correction for multiple tests).

Data were analysed using SAS for Windows, release 9.2 (SAS Institute Inc). Project management including data banking, quality control and statistical analysis, was performed by MEDIDATA (Modena, Italy).

Results

Linguistic validation of Italian version of MMAS-8

The MMAS-8 was translated into Italian and back-translated into English. The Italian translation for "treatment plan" (the seventh item of the second consensus version of MMAS-8), was considered difficult to understand; therefore it was decided to improve the description of this topic during the first comprehension test. Investigators reported the number of patients who found difficulties in the comprehension of questions and answer modality. The results of the first comprehension test are shown in Table 1. For items 2 and 8, only 4 and 2 patients, respectively, had difficulties in understanding the question, whereas answer modality used by many patients for item 1–7 was not consistent with instruction. Instruction for patients on the questionnaire was "please indicate the correct number" and the answer field was split in two columns with the header "YES = 0" and "NO = 1". Several patients (8 patients for items 1, 4, 5 and 7, and 11 patients for item 2) indicated their answer by writing an "X" under the proper column, while the majority of patients used a different answer modality, writing the number 0 or 1 in the answer field of the questionnaire. After this preliminary analysis, the wording of items 2 and 8 were modified and made more user-friendly by putting the question in first name terms; although patients understood item 7 and gave correct answer, physicians reported that eight patients asked for clarifications about the meaning of the term "treatment plan". We therefore decided to change the wording for "treatment plan", making it easier to understand: the new wording referred to the scheduling of doses and time of PD medications intake; moreover, question was putted in first name terms (second Italian MMAS-8 version). Instruction for patients was also modified in order to harmonize patient interpretation and answer modality. In the second Italian

Scala di Morisky sull'Aderenza al Farmaco (MMAS-8-Item).

Hai riferito che stai prendendo farmaci per la Malattia di Parkinson.
Alcuni pazienti hanno lamentato problemi legati al comportamento seguito nel prendere i farmaci e ci interessa conoscere la tua esperienza al riguardo.
Non ci sono risposte giuste o sbagliate.
Ti preghiamo di rispondere a ciascuna domanda in base alla tua personale esperienza con i farmaci per la Malattia di Parkinson.

(Si prega di indicare con una X la risposta)

	SI	NO
1. A volte dimentichi di prendere i tuoi farmaci per la Malattia di Parkinson?		
2. Alcune persone a volte saltano l'assunzione dei loro farmaci, ma non perché se lo dimenticano. Nelle ultime due settimane, ci sono stati giorni in cui non hai preso i tuoi farmaci per la Malattia di Parkinson?		
3. Hai mai diminuito le dosi o smesso di prendere i tuoi farmaci per la Malattia di Parkinson senza dirlo al tuo dottore, perché ti sentivi peggio quando li prendevi?		
4. Quando viaggi o vai via da casa, dimentichi a volte di portare con te i farmaci per la Malattia di Parkinson?		
5. Ieri hai preso i tuoi farmaci per la Malattia di Parkinson ?		
6. Quando senti che la Malattia di Parkinson è sotto controllo, ti capita a volte di smettere di prendere i tuoi farmaci?		
7. Per alcune persone prendere i farmaci ogni giorno è una vera seccatura. Dover prendere i tuoi farmaci per la Malattia di Parkinson a dosi fisse e all'orario giusto, ti ha mai infastidito?		

8. Quanto spesso sei in difficoltà a ricordare di prendere tutti i tuoi farmaci?

(Si prega di indicare con una x la risposta)

Mai/Raramente…… ❑
Una volta ogni tanto……❑
A volte…… ❑
Solitamente …… ❑
Continuamente ……❑

Fig. 1 Ownerships: all psychometric products as well as their translations, adaptations, computer programs, and scoring algorithms of the MMAS-8 are intellectual property of Donald E. Morisky, ScD, ScM, MSPH. ("Owner") Professor of Community Health Sciences, UCLA Fielding School of Public Health, Los Angeles, CA 90095-1772 and can be obtained through a license agreement with the Developer/Owner

MMAS-8, patients were asked to indicate with an "X" the correct answer; moreover, the headers of the columns in answer field were modified to "YES" and "NO". A second comprehension test was made in order to evaluate the effects of these changes. The new Italian MMAS-8 version was tested on 19 further PD patients and results are listed in Table 1. One patient missed answer modality for item 2–8: the patient reported "Yes" or "No" instead of the "X" under the proper column. The same patient reported to have difficulties to choose an answer representative of his condition for item 8. Two more patients found difficulties in answering item 5 as they seemed undecided about the answer to choose from: they put the "X" in a column but immediately stated that their answer was wrong and corrected the answer. These results showed an acceptable linguistic validity of the second Italian MMAS-8 version. The resulting final version of Italian MMAS-8 (see Fig. 1) was used in the REASON Study.

Evaluation of adherence to therapy

The study sample consisted of 776 patients, and 775 (99.9 %) of these met the inclusion criteria. There were 391 (50.5 %) early and 384 (49.5 %) advanced PD patients. Mean ± SD age was 69.0 ± 9.1 years; 469 (60.5 %) subjects were males, and mean ± SD MMSE score was 26.4 ± 3.4. Of the 775 patients included, 502 (64.8 %) had low educational level (≤8 years of grade school education). The mean ± SD PD duration was 5.1 ± 3.6 years in early PD patients, and 9.2 ± 5.4 years in advanced PD patients. The mean UPDRS total score was 24.6 ± 12.7 in early and 48.2 ± 19.4 in advanced PD

Table 1 First and second comprehension test results: percentage of the patients reporting difficulties in understanding questions or answer modes

Items	First comprehension test ($n = 30$)		Second comprehension test ($n = 19$)	
	Questions (%)	Answers mode (%)	Questions (%)	Answers mode (%)
1	0	26.7	0	0
2	13.3	36.7	0	5.2
3	0	30	0	5.2
4	0	26.7	0	5.2
5	0	26.7	0	15.8
6	0	30	0	5.2
7	0	26.7	0	5.2
8	6.7	3.3	5.2	5.2

patients, whilst the UPDRS part III score was, respectively, 16.2 ± 9.0 and 30.5 ± 13.0. Treatment duration was 4.1 ± 3.2 years in early and 8.1 ± 5.6 in advanced PD patients. Current anti-Parkinson therapy and concomitant treatments are detailed in Table 2.

According to the neurologist best guess, 96 % of the patients were adherent to therapy and 92 % were adherent to scheduled time of drug administration, with no clinically relevant difference of early vs advanced PD patients, low vs highly educated patients, patients needing vs not needing a change in therapy and patients with low vs medium MMAS-8 score (Table 3). Advanced PD patients were more likely than early ones (31 vs 10 %, respectively, χ^2, p value <0.0001) to adhere to therapy thanks to caregiver. The caregiver played an important role in therapy administration also in relation to level of education: for 26 % of patients with low educational qualifications (none/primary school) adherence depended on caregiver compared to 20 and 14 % of middle school and high school/academic degree, respectively (χ^2, p value = 0.0027). As for neurologists' opinion, 4 % of patients abused drugs (anti-PD treatment) with no differences according to disease severity, educational level or patients with low vs medium MMAS-8 score (see Table 3). Moreover, no difference was detected in adherence to therapy as for neurologist between males and females (data not shown).

The analysis of the MMAS-8 scale was carried out on 773 of the 775 patients (two patients were excluded from the analyses because they had more than two MMAS-8 scale missing items). Patients with low and medium adherence to therapy according to MMAS-8 score were 235 (30 %) and 538 (70 %), respectively. No patient had MMAS-8 score equal to eight, meaning *high* adherence. The mean ± SD total MMAS-8 score was 6.1 ± 1.2; no clinically relevant difference in total MMAS-8 scores emerged between early and advanced PD patients, or

Table 2 Ongoing drug therapies in Parkinsonian patients

	Totals ($n = 775$)	Early PD patients ($n = 391$)	Advanced PD patients ($n = 384$)
APD, *n* (%)			
LD monotherapy	165 (21.3)	82 (21.0)	83 (21.6)
LD + entacapone	64 (8.3)	23 (5.9)	41 (10.7)
DAs monotherapy	141 (18.2)	111 (28.4)	30 (7.8)
LD + Das	255 (32.9)	120 (30.7)	135 (35.2)
LD + DAs + entacapone	130 (16.8)	40 (10.2)	90 (23.4)
Other APD	20 (2.6)	15 (3.8)	5 (1.3)
Not PD-specific drugs, *n* (%)			
Antidepressants	125 (16.1)	65 (16.6)	60 (15.6)
Benzodiazepine	75 (9.7)	37 (9.5)	38 (9.9)
Atypical neuroleptics	29 (3.7)	5 (1.3)	24 (6.3)
Other not PD-specific therapies	79 (10.2)	34 (8.7)	45 (11.7)

Early PD patients: HY staging 1–2; Advanced PD patients: HY staging 2.5–4. Other APD: anticholinergics, MAO-B inhibitors, amantadine, tolcapone. Other not PD-specific therapies = typical neuroleptics, hypnotics, antiemetics and antinauseants, gastroprotective drugs, laxatives, anti-inflammatory or painkillers, orthostatic hypotension drugs, other psychiatric therapies

APD anti-parkinson drugs, *LD* levodopa (levodopa + carbidopa, levodopa + carbidopa extended release, levodopa + benserazide, levodopa + benserazide extended release, melevodopa + carbidopa), *DAs* dopamine agonist agents (pramipexole, pramipexole extended release, ropinirole, ropinirole extended release, rotigotine, pergolide, cabergoline, apomorphini hydrocloridum, other dopamine agonist agent)

Table 3 Adherence to drug therapy for PD according to neurologist and patient opinion

	Total ($n = 775$)	Early PD patients ($n = 391$)	Advanced PD patients ($n = 384$)	p value	Change of therapy at baseline		p value	Education			p value	Adherence to therapy (according to MMAS-8)		p value
					Yes ($n = 255$)	No ($n = 520$)		None/ primary school ($n = 318$)	Middle school ($n = 184$)	High school/ academic degree ($n = 256$)		Low ($n = 235$)	Medium ($n = 538$)	
Patients adherent to therapy (%)	96	98	94	0.0028	94	97	0.0111	96	96	97	0.6409	94	98	0.0022
Patients adherent to scheduled time of drug administration (%)	92	95	90	0.0214	90	94	0.0997	93	89	94	0.0577	86	95	<0.0001*
Patients who abuse of drug (%)	4	3	5	0.3294	6	3	0.1352	4	5	3	0.3445	4	4	0.8744
Patients adherent thanks to caregiver (%)	20	10	31	<0.0001*	21	20	0.5911	26	20	14	0.0027	24	18	0.0491
MMAS-8 score (mean ± SD)	6.1 ± 1.2	6.2 ± 1.2	6.0 ± 1.3	0.01678	6.0 ± 1.3	6.2 ± 1.2	0.02754	6.1 ± 1.2	6.0 ± 1.2	6.1 ± 1.3	0.5808			

Early PD patients: HY staging 1–2; Advanced PD patients: HY staging 2.5–4. Low adherence: MMAS-8 score <6; Medium adherence: MMAS-8 score between 6 and <8

* χ^2 test, t test or ANOVA p value < 0.002, alpha with Bonferroni correction

according to different degrees of education or change of therapy at baseline (see Table 3). Moreover, no difference was detected in MMAS-8 score between males and females (data not shown) and when comparing patients with MMSE score <26 and ≥26 (mean ± SD 6.0 ± 1.4 and 6.2 ± 1.2, respectively; p value t test = 0.128).

A significant association was present between total MMAS-8 score and disease duration: patients with disease duration <2 years had a mean ± SD MMAS-8 score of 6.4 ± 1.0 that was significantly higher than that observed in patients with 2–9 and >9 years disease duration (mean ± SD scores: 6.1 ± 1.3 and 5.9 ± 1.3, respectively; ANOVA, p value 0.0007).

Considering the frequency distribution of MMAS-8 items, 90 % of patients answered that they had consumed medicines for PD the day before the visit, 65 % stated that they did not have difficulties in remembering to take all the medicines, 30 % felt bothered about sticking to the treatment plan, 33 % sometimes forgot to take PD medicines, 10 % had not taken medications during the last 2 weeks for reasons other than forgetting and 9 % had stopped taking the medications without telling the doctor, because they felt worse after drug intake.

Discussion

In this study, we completed the translation of the MMAS-8 scale in the Italian language. This process was considered necessary as there was no validated Italian scale to assess drug compliance in PD patients in everyday clinical practice. To achieve the greatest effectiveness for self-assessment instruments, it is essential that the translation takes into account not only linguistic factors but also cultural components [12]. This procedure was carried out according to standardized procedures and after a multi-step process with corrections and adjustments, we produced the current version that was shown to be comprehensible by PD patients.

The second aim of our work was to study the usefulness of the translated scale to measure adherence to therapy in PD patients. We enrolled a large sample of PD patients from different outpatient clinics at highly specialized centres, with a well-balanced distribution of disease severity as measured by the HY stage. We found that the neurologists judged that a very high proportion of patient (>90 %) had high compliance, a result similar to that reported by Valldeoriola [4]. MMAS-8 showed medium adherence in 70 % of PD patients, no patient had high adherence. When compared to the few studies that used the MMAS questionnaires in PD patients, Elm [9] found a good correlation between MMAS-4 scores and pill count, whereas Valldeoriola [4] found that only about 60 % of the

patients showed good adherence to therapy. It must be underlined, however, that Valldeoriola [4], used the MMAS-4 item questionnaire; whereas in our study we administered the 8-item questionnaire that has been shown to have greater reliability than the 4 item measure. The mean MMAS-8 score we observed in our study is comparable to scores obtained in previous studies performed in other clinical conditions such as hypertension and diabetes [18, 19]. In our study, adherence to therapy did not differ with respect to gender, severity of disease, education, or decision to change or maintain the treatment; whereas a significant inverse association was observed between MMAS-8 score and duration of disease, with lower duration of the disease associated with better compliance, an observation likely explained by the difficulties that patients may encounter with the complexity of treatment in the advanced phases of the disease. Finally, in Valldeoriola [4] adherence to therapy negatively correlated with cognitive dysfunction; in REASON study almost a third of sample had cognitive dysfunction according to MMSE and we found no difference in MMAS-8 score when comparing patients with MMSE score <26 versus ≥ 26.

A limitation of the study is that we used the Italian MMAS-8 questionnaire only in PD patients and did not compare the results with those of patients with other chronic conditions.

In conclusion, we have provided Italian clinical practice with a validated new instrument for assessing treatment adherence, i.e. the Italian version of the MMAS-8. PD patients were able to complete the questionnaire that was also easy and fast to administer. Adherence to therapy in our PD patients was medium, comparable to that seen in other chronic conditions.

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Conflict of interest The authors declare that they have no conflict of interest.

Appendix: The REASON study group

Steering committee:

- Giovanni Abbruzzese, Dipartimento di Neuroscienze, Oftalmologia e Genetica—Università di Genova, Italy.
- Angelo Antonini, Department for Parkinson's Disease, IRCCS San Camillo, Venice, Italy.
- Paolo Barone, Scuola Medica Salernitana, Università degli Studi di Salerno, Salerno, Italy.
- Roberto Ceravolo, Dipartimento di Neuroscienze Azienda Ospedaliero-Universitaria Pisana, Italy.
- Giovanni Fabbrini, Sapienza Università di Roma, and Neuromed Institute, Pozzilli (IS), Italy.
- Michele Tinazzi, Dipartimento di Scienze Neurologiche, Neuropsicologiche, Morfologiche e Motorie, Università di Verona, Italy.

Participating centres:

- **M. A. B. Melone**, C. Schettino, F. Califano, Az. Osp. Univ. Seconda Universtà di Napoli (Napoli).
- **M.G. Ceravolo**, M. Capecci, E. Andrenelli, Az. Ospedali Riuniti (Ancona);
- **F. Iemolo**, D. Spadaro, A. Carnemolla, Ospedale Civile R. Guzzardi (Vittoria);
- **F. E. Pontieri**, C. Pellicano, D. Benincasa, Az. Osp. Sant'Andrea (Roma);
- **G. Fabbrini**, S. Pietracupa, A. Latorre, Sapienza Università di Roma (Roma);
- **G. Tedeschi**, A. Tessitore, A. Giordano, Seconda Università Federico II (Napoli);
- **U. Bonuccelli**, D. Frosini, F. Vanelli, Ospedale Santa Chiara (Pisa);
- **G. Comi**, M. A. Volonté, F. Spagnolo, Fondazione Centro San Raffaele (Milano);
- **A. Scaglioni**, G. Abrignani, Ospedale di Vaio (Fidenza);
- **G. Abbruzzese**, L. Avanzino, T. Tamburini, Università degli Studi di Genova (Genova);
- **A. Antonini**, S. Facchini, R. Biundo, Ospedale San Camillo (Venezia Lido);
- **M. C. Altavista**, C. Roberti, Ospedale San Filippo Neri (Roma);
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- **T. Avarello**, Az. Osp. Riuniti Villa Sofia-Cervello (Palermo);
- **G. Bono**, G. Riboldazzi, S. Leva, Ospedale di Circolo e Fondazione Macchi (Varese);
- **M. Del Sette**, E. Carabelli, E. Traverso, Ospedale Sant' Andrea (La Spezia);
- **R. Michelucci**, S. Nassetti, E. Pasini, Ospedale Bellaria (Bologna);
- **A. Padovani**, E. Cottini, B. Bigni, Az. Osp. Spedali Civili (Brescia);
- **S. Ruggieri**, N. Modugno, M. Fischetti, Istituto Mediterraneo Neuromed (Pozzilli);
- **A. Stefani**, M. Pierantozzi, M. Stampanoni Bassi, Policlinico Tor Vergata (Roma);
- **M. Tinazzi**, S. Ottaviani, D. Ajena, Ospedale Civile Maggiore—Borgo Trento (Verona);
- **G. Trianni**, F. My, M. Caggiula, Ospedale Vito Fazzi (Lecce);

- **G. Valenti**, S. Grioli, I. La Farina, Ospedale Garibaldi (Catania);
- **S. Zambito Marsala**, C. Marchini, M. Gioulis, Ospedale San Martino (Belluno);
- **P. Barone**, M. Picillo, M. Moccia, Università Federico II Napoli (Napoli);
- **A. Denaro**, L. Sebastianelli, Istituto Chirurgico Ortopedico Traumatologico (Latina);
- **M. Onofrj**, A. Thomas, Fondazione Università Gabriele D'Annunzio (Chieti);
- **C. Marini**, F. De Santis, V. Spagnoli, Ospedale di Avezzano (Avezzano);
- **R. L'Erario**, P. Passadore, Ospedale S. Maria della Misericordia (Rovigo);
- **E. Belgrado**, M. Mucchiut, Az. Osp. Univ. S.Maria della Misericordia (Udine);
- **A. Priori**, F. Cogiamanian, Fondazione Ospedale Maggiore Policlinico (Milano);
- **A. Marchet**, Ospedale Martini (Torino).

Sponsorship:

- Patrizia Lessi, Boehringer-Ingelheim, Milano, Italy.

Project Management, Statistical Analyses and data management:

- MediData Studi e Ricerche, Modena: G. Castegnaro, A. Ori, S. Pirondi, S. Rizzoli, B. Roncari, S. Sala, S. Sgarbi, L. Simoni, F. Trevisan, L. Zanoli.

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