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**Randomized controlled trial of a home-based palliative approach for people with severe multiple sclerosis**

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**Randomized controlled trial of a home-based palliative approach for people with severe multiple sclerosis**

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Complete List of Authors:	Solari, Alessandra; Foundation IRCCS Neurological Institute C. Besta, Unit of Neuroepidemiology Giordano, Andrea; Foundation IRCCS Neurological Institute C. Besta, Unit of Neuroepidemiology Patti, Francesco; University Hospital Policlinico Vittorio Emanuele, Neurology Clinic, MS Center Grasso, Maria Grazia; IRCCS S. Lucia Foundation, Multiple Sclerosis Unit CONFALONIERI, PAOLO; Foundation IRCCS Neurological Institute C. Besta, Department of Neuroimmunology and Neuromuscular Diseases Palmisano, Lucia; Istituto Superiore di Sanita, National Center for Drug Evaluation and Research Ponzio, Michela; Italian Multiple Sclerosis Foundation (FISM), Scientific Research Area Borreani, Claudia; Foundation IRCCS Istituto Nazionale per la Cura dei Tumori, Unit of Clinical Psychology Rosato, Rosalba; University of Turin, Department of Psychology Veronese, Simone; FARO Charitable Foundation, - Zaratin, Paola; Italian Multiple Sclerosis Foundation (FISM), Scientific Research Area Battaglia, Mario; University of Siena, Department of Life Sciences
Keywords:	Multiple sclerosis, Palliative care, Randomized controlled trial, Quality of Life, Symptom burden, Caregivers
Abstract:	Background: Evidence on the efficacy of palliative care in persons with severe multiple sclerosis (MS) is scarce. Objective: To assess the efficacy of a home-based palliative approach (HPA) for adults with severe MS and their carers. Methods: Adults with severe MS-carer dyads were assigned (2:1 ratio) to either HPA or usual care (UC). At each center, a multi-professional team delivered the six-month intervention. A blind examiner assessed dyads at

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	<p>baseline, three and six months. Primary outcome measures were Palliative care Outcome Scale-Symptoms-MS (POS-S-MS), and Schedule for the Evaluation of Individual Quality of Life-Direct Weighting (SEIQoL-DW, not assessed in severely cognitively compromised patients).</p> <p>Results: Of 78 dyads randomized, 76 (50 HPA, 26 UC) were analyzed. Symptom burden (POS-S-MS) significantly reduced in HPA group compared to UC (<math>p=0.047</math>). Effect size was 0.20 at three, 0.32 at six months, and statistical significance borderline in per-protocol analysis (<math>p=0.062</math>). Changes in SEIQoL-DW index did not differ in the two groups, as changes in secondary patient and carer outcomes.</p> <p>Conclusions: HPA slightly reduced symptoms burden. We found no evidence of HPA efficacy on patient quality of life, and on secondary outcomes.</p> <p>Trial registration number: ISRCTN73082124.</p>

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10 **Authors:**

11  
12 Alessandra Solari<sup>1\*</sup>, Andrea Giordano<sup>1</sup>, Francesco Patti<sup>2</sup>, Maria Grazia Grasso<sup>3</sup>, Paolo Confalonieri<sup>4</sup>,  
13  
14 Lucia Palmisano<sup>5</sup>, Michela Ponzio<sup>6</sup>, Claudia Borreani<sup>7</sup>, Rosalba Rosato<sup>8</sup>, Simone Veronese<sup>9</sup>, Paola  
15  
16 Zaratini<sup>6</sup>, Mario Alberto Battaglia<sup>10</sup>, on behalf of the PeNSAMI project\*  
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19  
20  
21  
22 1. Unit of Neuroepidemiology, Foundation IRCCS Neurological Institute C. Besta, Via Celoria 11,  
23  
24 20133 Milan, Italy

25  
26  
27 2. MS Centre, Neurology Clinic, University Hospital Policlinico Vittorio Emanuele, Via S. Sofia 78,  
28  
29 95123 Catania, Italy

30  
31 3. Multiple Sclerosis Unit, IRCCS S. Lucia Foundation, Via Ardeatina 306, 00179 Rome, Italy

32  
33 4. Department of Neuroimmunology and Neuromuscular Diseases, Foundation IRCCS  
34  
35 Neurological Institute C. Besta, Via Celoria 11, 20133 Milan, Italy

36  
37  
38 5. National Center for Drug Evaluation and Research, Istituto Superiore di Sanità, Viale Regina  
39  
40 Elena 299, 00161 Rome, Italy

41  
42  
43 6. Scientific Research Area, Italian Multiple Sclerosis Foundation (FISM), Via Operai 40, 16149  
44  
45 Genoa, Italy

46  
47  
48 7. Unit of Clinical Psychology, Foundation IRCCS Istituto Nazionale per la Cura dei Tumori, Via  
49  
50 Venezian 1, 20133 Milan, Italy

51  
52 8. Department of Psychology, University of Turin, Via Verdi 10, 10125 Turin, Italy

53  
54 9. FARO Charitable Foundation, Via Morgari 12, 10125 Turin, Italy

55  
56  
57 10. Department of Life Sciences, University of Siena, Via Banchi di Sotto 55, 53100 Siena, Italy  
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1  
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3 \* Members listed in Appendix  
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5  
6  
7

8 **Corresponding author:**

9  
10 Alessandra Solari, MD

11  
12 Unit of Neuroepidemiology

13  
14 Foundation IRCCS Neurological Institute C. Besta

15  
16 Via Celoria 11,

17  
18 20133 Milan, Italy

19  
20 E-mail: [alessandra.solari@istituto-besta.it](mailto:alessandra.solari@istituto-besta.it)

21  
22 Tel. +39 02 23944016; Fax +39 02 23944056  
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31 symptom burden, caregivers.  
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34 **Running title:** Home-based palliative approach for people with severe multiple sclerosis.  
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**ABSTRACT**

**Background:** Evidence on the efficacy of palliative care in persons with severe multiple sclerosis (MS) is scarce.

**Objective:** To assess the efficacy of a home-based palliative approach (HPA) for adults with severe MS and their carers.

**Methods:** Adults with severe MS-carer dyads were assigned (2:1 ratio) to either HPA or usual care (UC). At each center, a multi-professional team delivered the six-month intervention. A blind examiner assessed dyads at baseline, three and six months. Primary outcome measures were Palliative care Outcome Scale-Symptoms-MS (POS-S-MS), and Schedule for the Evaluation of Individual Quality of Life-Direct Weighting (SEIQoL-DW, not assessed in severely cognitively compromised patients).

**Results:** Of 78 dyads randomized, 76 (50 HPA, 26 UC) were analyzed. Symptom burden (POS-S-MS) significantly reduced in HPA group compared to UC ( $p=0.047$ ). Effect size was 0.20 at three, 0.32 at six months, and statistical significance borderline in per-protocol analysis ( $p=0.062$ ). Changes in SEIQoL-DW index did not differ in the two groups, as changes in secondary patient and carer outcomes.

**Conclusions:** HPA slightly reduced symptoms burden. We found no evidence of HPA efficacy on patient quality of life, and on secondary outcomes.

**Trial registration number:** ISRCTN73082124.

## INTRODUCTION

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Around 15% of multiple sclerosis (MS) patients have a progressive course from the outset, and a further 35% develop progressive disease after a variable period with relapsing disease (secondary progressive MS) [1]. International, multi-stakeholder initiatives have recently increased the focus on progressive MS, with the mission to speed up the development of therapies for people with this challenging disease form, most of whom are severely disabled for many years [2,3].

Alignment of treatment with the patient's needs, values and preferences, a core element of shared decision-making and palliative care (PC), should be routine aspect of care of any health professional (HP) and in any care setting. The provision of PC services, irrespective of diagnosis and illness stage, has been advocated, together with the development of such services for patients with neurological diseases [4-6]. In this context the integration of neurology, PC and rehabilitation competencies is key, as well as the individualized care provided by each discipline along the disease trajectory [7,8]. A consensus review concluded that there is limited evidence for the provision of PC for patients with progressive neurological diseases, and that further research into this area of care is urgently needed [9]. Two randomized controlled trials (RCTs) have been published on this regard: a UK trial on 52 MS patient-caregiver dyads comparing a three-month specialist PC service to standard care found no effect on the primary

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9 outcome (emotional, psychological, and spiritual needs of MS patients). Nevertheless,  
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11 some symptoms improved and informal caregiver burden was reduced compared to  
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13 standard care [5]. The other (NE-PAL) RCT compared a four-month home specialist PC  
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15 service to standard care in 50 people with advanced neurodegenerative disorders, 36%  
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17 of whom had MS. The intervention significantly improved patient quality of life and  
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19 some symptoms compared to standard care; but there was no effect on caregiver  
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21 burden [10].  
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25 We performed a multicenter RCT involving adults with severe MS and their carers to  
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27 assess the effectiveness of a home-based palliative approach (HPA) added to usual  
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29 care (UC). As for the RCTs reported above, we applied the framework for  
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31 development/efficacy testing of complex interventions [11]. The results of the RCT are  
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33 presented, except for the economic analysis and the nested qualitative study which  
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35 will be presented in separate papers.  
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## 41 **METHODS**

### 42 **Study design and participants**

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45 In this randomized, examiner-blind, controlled study, we recruited patients from three  
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47 Italian centers. The protocol was approved by the local ethics committees and the  
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9 study was undertaken in accordance with the Declaration of Helsinki [12]. The trial was  
10 registered at [www.controlled-trials.com](http://www.controlled-trials.com) (ISRCTN73082124).

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13 Participants were non-institutionalized adults (age  $\geq 18$  years) with severe MS and  
14 their primary carers. Other patient inclusion criteria were primary or secondary  
15 progressive MS [1,13], Expanded Disability Status Scale (EDSS) score  $\geq 8.0$  [14],  
16 complex symptoms [15], and  $\geq 2$  unmet care needs [16]. The carer (a family member,  
17 relative, or friend of the patient) was his/her next of kin, and was designated by the  
18 patient except for patients with severe cognitive compromise. All patient-carer dyads  
19 gave written informed consent before study enrolment.  
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### 32 **Randomization and masking**

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34 Dyads were randomly assigned (2:1) to receive HPA or UC. Allocation to treatment  
35 groups was done using a third-party, web-based computerised randomisation  
36 procedure with stratified minimization for: EDSS score (8.0-8.5, 9.0-9.5), presence of  
37 severe cognitive compromise (clinical judgement), and center.  
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44 The trial senior statistician (RR) was not involved in study conduct. The blind examiners  
45 used a web-based case report form (eCRF), so that visit 1-3 data were available to HPA  
46 teams and coordination unit. After visits 2 and 3, examiners were asked to guess dyad  
47 assignment.  
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## Intervention

Based on the principles of PC [17], each center had a HPA team consisting of a physician (neurologist or physiatrist), a nurse (case manager and team leader), a psychologist, and a social worker. Nurses of the Milan and Rome centers had degrees and worked full time in PC; the Catania nurse attended a week-long individual training course. Prior to study start, all team members were trained in the HPA intervention; three and six months after trial initiation they met again to share experiences, fine-tune the protocol, and discuss difficult cases.

After a comprehensive assessment of the dyad needs based on direct observation and on visit 1 information (available via the eCRF), the HPA team defined the contents of the intervention, involving the dyad and the patient caring physician (the intervention was not intended to replace existing services). Subsequently, the team verified program implementation, and reviewed it as necessary. The team was not on call for dyads: in the event of emergencies, dyads contacted the patient caring physician or emergency medical services. All team activities were recorded in the PeNSAMI patient study record, which was kept at the patient's home and available to all HPs/caregivers.

UC consisted of the health and social services provided by the Italian National Health Service in the study area. Dyads assigned to UC received the three examiner visits

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9 (visits 1-3) and the monthly telephone interviews, but not the HPA team visits (except  
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11 visit 0). At the end of the study, dyads who received UC were offered the HPA.  
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### 14 15 16 **Outcomes**

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18 The pre-specified primary endpoints were changes in patient quality of life (SEIQoL-  
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20 DW) and symptom burden (PC Outcome Scale-Symptoms-MS, POS-S-MS). The SEIQoL-  
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22 DW is administered in an interview in which respondents nominate the five areas of  
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24 life that are most important in determining their QOL, and rate the  
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26 satisfaction/functioning and weight/importance in each of these areas [18]. The  
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28 SEIQoL-DW index can range from 0 to 100 (best).  
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32 The POS-S-MS (primary outcome measure) and the core POS were developed and  
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34 validated for use in PC [18,19]. POS consists of 10 items addressing emotional,  
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36 psychological and spiritual needs, and provision of information and support, each  
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38 scored from 0 to 4; POS total score can range from 0 to 40 (worst). POS-S-MS  
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40 comprises 20 items relating to MS symptom burden (0 to 4 scale) plus an open  
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42 question. Following advice of the POS-S-MS authors, we used the 17 pre-set items  
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44 (POS-S-MS total score possible range 0 to 68 [worst]) [20]. For both core POS (version  
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46 1) and POS-S-MS [<http://pos-pal.org/maix/>] we used the preceding seven days' time  
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9 frame, and caregiver version of the scales in patients with severe cognitive  
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11 impairment.

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13 In addition to core POS, patient secondary outcome measures were: the European  
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15 Quality of life Five Dimensions (EQ-5D-3L) [21], the Hospital Anxiety and Depression  
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17 Scale (HADS) [22], the Functional Independence Measure (FIM) [23], and direct and  
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19 indirect tangible costs (assessed by the MS foundation Costs Questionnaire, MSCQ)  
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21 [24]. Carer outcomes were: the Short Form 36 (SF-36) [25], the EQ-5D-3L, the HADS,  
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23 and the Zarit Burden Interview (ZBI) [26].  
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### 30 **Statistical analysis**

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32 The sample size was based on previous data for POS-S-MS [5] and SEIQoL-DW [10]. We  
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34 expected that up to 50% of MS patients would have not be able to complete the  
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36 SEIQoL-DW (severe cognitive compromise); in these the only primary endpoint was the  
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38 POS-S-MS (caregiver version).  
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42 For the POS-S-MS, we calculated that a sample size of 62 patients would yield a power  
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44 of 85% to detect a mean score change of  $-0.4$  (SD 0.5) in the HPA group compared to a  
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46 change of  $0.2$  (SD 0.8; null hypothesis) in the UC group, at an  $\alpha$  level of 0.05 [5].  
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49 Assuming 20% dropout, 49 patients were required in the HPA group and 25 patients in  
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51 the UC group (total sample size 74).  
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9 For the SEIQoL-DW, we calculated that a sample size of 32 patients would yield a  
10 power of 80% to detect a mean score change of 12.1 (SD 12.8) in the HPA group  
11 compared to a change of -7.4 (SD 19.3) in the UC group, at an  $\alpha$  level of 0.05 [10].  
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15 Assuming 20% dropout, 25 patients were required in the HPA group and 13 in the UC  
16 group (total sample size 38).  
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20 All randomly assigned patients were included in the main intention-to-treat analysis,  
21 provided that at least one contact with the team occurred (HPA group). We compared  
22 the outcome score changes in the intervention groups by use of general linear model  
23 adjusting for baseline score. Missing data were imputed according to Rubin's multiple  
24 imputation approach. A per-protocol analysis was also done for the primary outcomes  
25 and all secondary outcomes, and included patients who accomplished the outcome  
26 measures. For analysis of patient outcomes POS-S-MS, POS, and FIM, we used the  
27 following covariates: center, presence of severe cognitive impairment, and age  
28 (baseline EDSS score was not included in the model as it was associated with cognitive  
29 impairment). For analysis of patient outcomes SEIQoL-DW and HADS, we used the  
30 covariates center, baseline EDSS score, and age. We also tested for the first-order  
31 interaction term center per intervention group. For analysis of the ZBI total score, we  
32 used the covariates and interaction term reported above (first set of patient  
33 outcomes), plus carer's age and gender, and carer living with the patient. Two-sided p  
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9 values of less than 0.05 were judged to be significant; p values were not adjusted for  
10 multiple comparisons. Analyses were done with Stata (version 13.0) and SAS (version  
11 9.4).  
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## 16 17 18 **RESULTS**

### 19 **Dyad enrolment and characteristics**

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22 Between January-November 2015, 50 dyads assigned to receive HPA and 26 assigned  
23 to receive UC were analysed (figure 1). Table 1 illustrates participant demographic and  
24 clinical characteristics at baseline.  
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32 [Insert table 1 about here]  
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### 37 **HPA team activities**

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39 Overall there were 360 home visits, 269 (75%) by one HP, 85 (24%) by two, and six  
40 (2%) by three or four HPs. On average dyads received 4.9 home visits in the first three  
41 months, and 2.8 in the second three months. The nurse (team leader) performed 152  
42 visits (33%), followed by the psychologist (25%), the physician (25%), and the social  
43 worker (17%). Figures were well balanced across centers (table 2) except for the  
44 number of visits performed by two or more HPs (Milan 4%, Rome 14%, Catania 51%;  
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9 p<0.001). Time from randomization to HPA team assessment was shorter in Catania  
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11 (median 8 days) compared to Milan (11 days) and Rome (12.5 days; p=0.11).  
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13 [Insert table 2 about here]  
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18 Figure 2 reports the pre-specified care needs [16] addressed by the HPA teams, and  
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20 those fulfilled at the end of the intervention, based on team reports. The most  
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22 addressed care needs belonged to the domain 'managing everyday life' (38%),  
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24 followed by 'organization' (34%) and 'psychosocial' (27%). A partial or complete  
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26 fulfilment was reported for most 'managing everyday life' needs (97%), but for  
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28 'organization' (73%) and 'psychosocial' (72%) dimensions fulfilment was lower,  
29  
30 particularly for 'access to services' and 'emotional wellbeing' categories. These  
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32 patterns appeared quite similar across the centers (online supplementary figure). In no  
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34 instance spiritual needs were identified (or addressed). Discussion about advance care  
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36 directives and end of life decisions was reported for two patients.  
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#### 44 **Primary outcomes**

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46 Mean change in POS-S-MS score from baseline to three months was 1.1 (95% CI -0.5 to  
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48 2.7) in the HPA group and -0.2 (95% CI -2.9 to 2.6) in the UC group, with a mean  
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50 between-group difference of -1.3 (95% CI -1.7 to 4.2), and a Cohen's *d* effect size (ES)  
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9 of 0.20. Mean change in POS-S-MS from baseline to six months was 2.3 (95% CI 0.4 to  
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11 4.1) in the HPA group and 0.3 (-2.0 to 2.6) in the UC group, with a mean between-  
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13 group difference of -1.9 (95% CI -1.1 to 5.0), and an ES of 0.32 (figure 3). The pre-  
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15 specified multivariate analysis is reported in table 3: HPA significantly reduced  
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17 symptom burden ( $p=0.047$ ), and there was no interaction between intervention and  
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19 center ( $p=0.62$ ). In the per-protocol analysis (supplementary table 1) the HPA effect on  
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21 POS-S-MS was of borderline statistical significance ( $p=0.062$ ).  
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32 The SEIQoL-DW interview was administered to 62 patients (82%; 41 HPA, 21 UC)  
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34 without severe cognitive impairment. Mean change in SEIQoL-DW index score from  
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36 baseline to three months was -0.9 (95% CI -6.8 to 5.1) in the HPA group and -3.7 (-17.6  
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38 to 10.3) in the UC group, with a mean between group difference of 2.8 (95% CI -12.2 to  
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40 17.8; ES 0.11). Mean change in SEIQoL-DW from baseline to six months was -0.8 (95%  
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42 CI -5.3 to 6.9) in the HPA group and 4.0 (-21.1 to 13.1) in the UC group, with a mean  
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44 between-group difference of 4.8 (95% CI -13.2 to 22.7; ES 0.10; figure 3). In the pre-  
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46 specified multivariate analysis, HPA had no significant effect on the primary outcome  
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48 ( $p=0.57$ ), and there was no interaction between intervention and center ( $p=0.70$ ; table  
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9 3). Findings from the per-protocol analysis matched those of the main analysis (online  
10 supplementary table 1).  
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### 13 14 15 16 **Serious adverse events and attrition**

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18 There were 22 serious adverse events (table 4) in 20 patients, 15 events in 13 patients  
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20 on HPA (30%) and seven events in seven patients on UC (27%;  $p=0.78$ ). Three HPA  
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22 patients died, all deaths were deemed to be unrelated to the intervention. Three  
23  
24 dyads discontinued the intervention, one in the HPA group and two in the UC group  
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26 (figure 1); one HPA dyad completed the intervention but did not perform visit 3.  
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32 [Insert table 4 about here]  
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### 37 **Other patient outcomes**

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39 We found no significant difference between intervention groups for change at three  
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41 and six months in POS, HADS Anxiety and Depression, and FIM total score (table 3).  
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43  
44 Two patients with baseline EDSS 8.0 worsened to EDSS 8.5 at three and six months  
45  
46 visits (one from each intervention group), the other remained unchanged (data not  
47  
48 shown). Per protocol analysis of secondary patient outcomes are reported in the  
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50 online supplementary table 1.  
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### Caregiver burden and other carer outcomes

Mean change in ZBI score from baseline to three months was 1.1 (95% CI -1.7 to 3.9)

in the HPA group and -0.5 (-4.1 to 3.2) in the UC group, with a mean between group

difference of 1.6 (95% CI -3.1 to 6.2, ES 0.16). Mean change from baseline to six

months was 0.2 (95% CI -2.8 to 3.2) in the HPA group and 1.7 (-1.1 to 4.5) in the UC

group, with a mean between-group difference of -1.5 (95% CI -6.1 to 3.1, ES 0.16).

There was no effect of HPA on ZBI score ( $p=0.83$ ), or interaction between intervention

and center ( $p=0.20$ ; table 3). Per-protocol analysis findings matched those of the main

analysis (online supplementary table 2).

### Examiner's masking

At visit 2, examiners guessed dyad assignment correctly in 12/73 (17%), incorrectly in 6

(8%), and answered 'don't know' in 55 (75%). Figures at visit 3 were 14% for correct,

7% for incorrect, and 79% for 'don't know' answers. Examiners guessed the correct

assignment in both visits in four HPA dyads (9%) and one UC dyad (4%).

### DISCUSSION

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9 In this six-month RCT in severely affected MS adults, a home-based palliative approach  
10 reduced symptom burden as assessed using the multidimensional POS-S-MS (primary  
11 outcome measure). The size of HPA effect was small, manifested at the end of the  
12 study, and the statistical significance was borderline. Three patients died during the  
13 study, all belonging to HPA group. The independent data and safety monitoring  
14 committee confirmed the center principal investigator judgment that these deaths  
15 were unrelated to the intervention. One further patient died immediately after  
16 baseline visit and the day before randomization, and one in the trial screening phase  
17 (figure 1).  
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21 Reduction of symptom burden was in line with evidence from the UK trial, which found  
22 improvement in a subset of five POS-S-MS symptoms (pain, nausea, vomiting, mouth  
23 problems and sleeping difficulty) [5]. We identified no evidence of efficacy of the  
24 intervention for the SEIQoL-DW (primary outcome measure), or for secondary patient  
25 (POS, HADS, FIM), and carer outcomes (22-item ZBI, SF-36, HADS). Findings for  
26 caregiver burden were at odds with the UK trial, which found a significant  
27 improvement in those carers (13/26 in the PC group and 17/26 in the standard care  
28 group) who completed the 12-item ZBI [5]. It should be noted that findings on  
29 caregiver burden in PC interventions are conflicting, as highlighted by a recent  
30 systematic review and meta-analysis [27].  
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9 At main difference with the UK and Ne-Pal trials was that in PeNSAMI the teams  
10 involved did not originate from PC services, and this was not a specialist PC  
11 intervention [28]. The three HPA multi-professional teams were led by a nurse who  
12 received higher specialist training and worked full-time in PC (Milan and Rome) or had  
13 received PC training for the trial and worked full-time in MS rehabilitation (Catania);  
14 the physicians (one neurologist and two neurologists and physiatrists) and the other  
15 professionals were MS experts. The clinical characteristics of our patients were similar  
16 to those of the UK trial, but Ne-Pal included patients with other neurological  
17 conditions, and excluded patients with severe cognitive compromise [10]. As in the UK  
18 trial, the HPA teams addressed the identified needs of the dyads indirectly, by  
19 activating existing services or bringing them to the attention of the dyads, which was a  
20 major study challenge due to the fragmentation of care and silos working style of  
21 services [15,29]. This may have impacted the response to the intervention, which we  
22 originally hypothesized at three months. It is thus possible that as for the reduction in  
23 symptom burden (POS-S-MS) which manifested at six month visit (figure 3) the time of  
24 HPA care was insufficient to produce an effect on most outcome measures. Data from  
25 team records also documented a difficulty in HPA goal achievement especially for  
26 psychosocial and organizational issues, while for symptom management and activities  
27 of daily living needs were at least partially met in the six-month time frame (figure 2).  
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9 These issues also emerged from the focus group of the HPA teams conducted at the  
10 end of the trial (online supplementary box), and should be carefully considered in the  
11 design of future PC trials for MS patients, which should at best match with both service  
12 activation and the MS disease trajectory.  
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18 Other differences with the two published RCTs which inspired our study are the  
19 adoption of a multicenter design, and an examiner-blind design (the nature of the  
20 intervention prevented us from blinding patients and carers to their allocated group).  
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22 The latter made more complex (and burdensome) the study procedures: the SEIQoL-  
23 DW interview was not administered by the HPA team (team members could only  
24 access SEIQoL-DW data of the patient via the eCRF), and participants had sometimes  
25 difficulty in distinguishing HPA team and examiner roles. In addition, the examiner's  
26 visits (particularly the SEIQoL-DW interview), and the monthly telephone interviews  
27 may have produced some non-specific effect in the UC group, which might have  
28 moderated the occurrence of performance bias [30]. However, an examiner-blind  
29 design improves the quality of the study by preventing ascertainment bias [30]. Inter-  
30 rater reliability (in outcome ascertainment) was a minor issue as in Milan and Catania  
31 outcome measures were obtained by the center's main examiner only, and in Rome  
32 both trained examiners (main and backup) operated. We met our recruitment and  
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9 retention targets, and missing data on both patient and carer outcomes were <10% –  
10 well below our pre-specified hypothesis [12], and data of RCTs on PC [27,31].

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12 It is essential to have QOL as a primary outcome measure for a PC intervention [17].

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14 We chose the SEIQoL-DW interview as it is an individualized tool, preventing patient  
15 exposure to non-pertinent or frustrating items, and the oversight of significant QOL  
16 dimensions. Ne-Pal findings provided evidence of the feasibility of SEIQoL-DW  
17 administration in this disabled patient population, and good scale responsiveness [10].  
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21 However, in view of the PeNSAMI trial experience, this instrument may have a higher  
22 potential in the hands of the treating professionals (here the HPA team), as it can be  
23 used to elucidate patient values and priorities, and thus facilitate the setting of goals  
24 that are aligned to such values [32].  
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34 To conclude, PeNSAMI trial showed that six-month HPA slightly reduces MS symptom  
35 burden, but did not produce evidence of an effect on patient QOL, or on the  
36 multifaceted patient-carer needs. Moreover, our findings suggest that a PC  
37 intervention for patients with severe MS may need to be over a longer period than six  
38 months. The trial was designed and conducted to minimize the risk of bias, at the  
39 expense of some burden for patients, carers, and health professionals. The analysis of  
40 the qualitative study nested in the RCT, by addressing the living experiences of  
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9 participants, will supplement trial findings, identify the strengths and challenges of the  
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11 intervention, and contribute to improve intervention's contents, processes and timing.  
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## 14 15 16 **APPENDIX**

### 17 18 **PeNSAMI project Investigators**

19  
20 **Steering Committee:** R Amadeo: *Italian Multiple Sclerosis Society (AISM)*; A Giordano,  
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22 M Ponzio, MG Grasso, A Lugaresi, F Patti, G Martino: *Italian Multiple Sclerosis Society*  
23  
24 *(AISM), Genoa*; L Palmisano: *Istituto Superiore di Sanità, Rome*; S Veronese, P Zaratin,  
25  
26 MA Battaglia, A Solari.  
27

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29 **Data Management and Analysis Committee:** A Giordano; E Pagano (cost analysis):  
30  
31 *Unit of Cancer Epidemiology, "Città della Salute e della Scienza" University Hospital of*  
32  
33 *Turin and CPO Piemonte, Turin*; D Radice (statistician): *Division of Epidemiology and*  
34  
35 *Biostatistics, European Institute of Oncology, Milan*; M Farinotti, G Ferrari; A Solari, R  
36  
37 Rosato (statistician): *Department of Psychology, University of Turin.*  
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41 **Independent Data and Safety Monitoring Committee:** DJ Oliver (Chair): *University of*  
42  
43 *Kent, Rochester, Kent, UK*; E Pucci: *Neurology Unit, Ospedale Provinciale di Macerata,*  
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45 *Macerata*; L Tesio: *Department of Biomedical Sciences for Health, University of Milan,*  
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47 *Milan*; *The Istituto Auxologico Italiano, IRCCS, Milan.*  
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9 **Qualitative Analysis Panel:** E Bianchi, S Cilia: *University Hospital Policlinico Vittorio*

10 *Emanuele, Catania;* S Cipollari: *IRCCS S Lucia Foundation, Rome;* E Pietrolongo, M

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13 Giuntoli, C Borreani.

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15 **Literature Review Panel:** MG Grasso, L Palmisano, A Fittipaldo, A Giordano.

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17 **Intervention Panel:** C Cugno, R Causarano, P Morino: *'Ex Convento delle Oblate'*

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19 *Hospice, Local Health Unit of Florence, Florence;* S Veronese.

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22 **Enrolling Centers and Investigators:** *Foundation IRCCS Neurological Institute C Besta,*

23  
24 *Milan:* P Confalonieri, E Rossetti, AM Giovannetti, V Torri Clerici, A Totis, A Campanella,

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27 M Farinotti, A Fittipaldo, G Ferrari, R Mantegazza, A Giordano, A Solari; *IRCCS S Lucia*

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29 *Foundation, Rome:* MG Grasso, MC Stefanelli, I Rossi, L Tucci, F Ippoliti, G Morone, A

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32 Fusco; *University Hospital Policlinico Vittorio Emanuele, Catania:* F Patti, C Cavallaro, A

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35 Pappalardo, V Cascio, G Occhipinti, V Cimino, F Zagari.

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37 **Other Centers and Investigators:** *AIISM Liguria Region Rehabilitation Service, Genoa:*

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40 ML Lopes de Carvalho, M Giuntoli, R Motta, MA Battaglia; *G d'Annunzio University,*

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42  
43 *Chieti-Pescara, Chieti:* A Lugaresi, E Pietrolongo, M Onofri; *FARO Charitable*

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45  
46 *Foundation, Turin:* S Veronese, C Cugno; *Niguarda Ca' Granda Hospital, Milan:* R

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49 Causarano, D Da Col; *Antea Charitable Association, Rome:* G Casale, MC Stefanelli;

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52 *Foundation IRCCS Istituto Nazionale per la Cura dei Tumori, Milan:* C Borreani, E

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**DECLARATION OF CONFLICTING INTERESTS**

AS has been a board member of Biogen Idec and Novartis, and has received speaker honoraria from Genzyme, Merck Serono, the Fondazione Serono and Excemed. FP received honoraria for speaking activities from Bayer Schering, Biogen Idec, Merck Serono, Novartis, and Sanofi Aventis. He has served as advisory board member of the following companies: Bayer Schering, Biogen Idec, Merck Serono, and Novartis. MGG has received research funding from Merck Serono and consulting and speaking fees from Biogen Idec. PC has been a board member of Biogen Idec, received travel grants from Sanofi Aventis, Biogen Dompe' and Merck Serono. PZ and MAB are board members of the Fondazione Italiana Sclerosi Multipla (charitable organization). All other authors declare that they have no competing interests.

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For Peer Review

**Table 1.** Baseline characteristics of the 76 MS patient-carer dyads at baseline, by allocated group. There were no significant differences between the groups except for carer education ( $p=0.04$ ), and for SF-36 Mental Composite ( $p=0.02$ ).

Characteristic	Home palliative approach (N = 50)	Usual care (N = 26)
<i>MS patients</i>		
Women	31 (62)	12 (46)
Age (years) <sup>1</sup>	60.5 ± 9.7	56.8 ± 9.5
Education: No education completed	1 ( 2)	0
Primary (5–8 years)	19 (38)	10 (38)
Secondary (12–13 years)	20 (40)	10 (38)
College/University (14+ years)	10 (20)	6 (24)
Occupation: Employed	2 ( 4)	2 ( 7)
Retired (age)	9 (18)	1 ( 4)
Unemployed	0	1 ( 4)
Retired (disability)	39 (78)	22 (85)
Age at MS diagnosis (years) <sup>1</sup>	37.5 ± 13.8	35.7 ± 10.9
Severe cognitive compromise	9 (18)	5 (19)
SEIQoL-DW <sup>1,3</sup>	61.3 ± 21.5	59.5 ± 30.0
POS-S-MS <sup>1</sup>	23.7 ± 8.8	23.9 ± 8.4
POS <sup>1</sup>	12.1 ± 6.8	12.0 ± 7.2
EDSS <sup>2</sup>	8.5 (8.0–9.5)	8.5 (8.0–9.5)
FIM total <sup>1</sup>	49.3 ± 16.9	52.6 ± 22.0
HADS Anxiety <sup>1,3</sup>	6.4 ± 3.9	6.6 ± 3.9
Depression <sup>1,3</sup>	6.9 ± 4.4	7.1 ± 3.6
<i>Carers</i>		
Women	31 (62)	16 (61)
Age (years) <sup>1</sup>	60.1 ± 13.9	60.8 ± 11.1
Education: Primary (5–8 years)	18 (36)	7 (27)
Secondary (12–13 years)	16 (32)	16 (62)
College/University (14+ years)	16 (32)	3 (11)
Occupation: Employed/student	23 (46)	13 (50)
Retired (age)	19 (38)	6 (23)
Housewife	6 (12)	7 (27)
Unemployed	2 ( 4)	0
Relation: Spouse/partner	25 (50)	15 (58)
Parent	8 (16)	4 (15)
Other relative	7 (14)	6 (23)
Son/daughter	8 (16)	0
Paid caregiver	2 ( 4)	1 ( 4)
ZBI total score <sup>1</sup>	35.9 ± 15.3	34.1 ± 12.5
SF-36 Physical Composite <sup>1,4</sup>	44.4 ± 10.9	43.2 ± 11.8
Mental Composite <sup>1,4</sup>	38.4 ± 9.1	43.6 ± 10.9
HADS Anxiety <sup>1</sup>	9.3 ± 4.0	8.0 ± 4.4
Depression <sup>1</sup>	7.1 ± 4.1	7.0 ± 5.2

EDSS, Expanded Disability Status Scale; FIM, Functional Independence Measure; HADS, Hospital Anxiety and Depression Scale; MS, Multiple sclerosis; POS, Palliative care Outcome Scale; POS-S-MS, Palliative care Outcome Scale-Symptoms-Multiple Sclerosis; SEIQoL-DW, Schedule for the Evaluation of Individual Quality of Life-Direct Weighting; SF-36, Short Form 36; ZBI, Zarit Burden Interview.



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1. Mean  $\pm$  standard deviation.
2. Median (range).
3. Assessed in 41 (82%) home palliative approach and 21 (81%) usual care patients who had no severe cognitive impairment.
4. For five home palliative approach and two usual care carers, Physical and Mental Composites were not calculated, in all cases due to missing items.

For Peer Review

**Table 2.** Home palliative approach (HPA) team activities in the three participating centers. All activities (except for HPA team meetings) were performed at patient's home.

Characteristic	Milan	Rome	Catania	
	N (%)			
Dyads assessed	16	15	19	
Dyads who completed the first three months	16 (100%)	13 (87%)	18 (95%)	
Dyads who completed the second three months	16 (100%)	12 (80%)	17 (89%)	
Time from randomization to HPA team assessment (days) <sup>1</sup>	11.4, 11.0 (4–29)	13.5, 12.5 (3–28)	9.3, 8.0 (2–25)	
Dyads assessed >14 days from randomization	3 (20%)	5 (36%)	3 (16%)	
HPA team visits, months 1-3	79 (4.9 per dyad)	64 (4.9 per dyad)	89 (4.9 per dyad)	
HPA team visits, months 4-6	46 (2.9 per dyad)	28 (2.3 per dyad)	54 (3.2 per dyad)	
Number of professionals involved in the home visits:	1	120 (96%)	79 (86%)	70 (49%)
	2	5 (4%)	13 (14%)	67 (47%)
	3, 4	0 (0%)	0 (0%)	6 (4%)
Type of health professional: Nurse (team leader)	38 (29%)	36 (34%)	78 (34%)	
	Psychologist	38 (29%)	26 (25%)	54 (24%)
	Physician	24 (18%)	25 (24%)	66 (29%)
	Social worker	30 (23%)	18 (17%)	29 (13%)

1. Mean, median (range)

**Table 3.** Generalized linear models (intention to treat analysis) of patient outcomes and of the Zarit Burden Interview (ZBI). EDSS is Expanded Disability Status Scale, HPA is home palliative approach, UC is usual care. All estimates are adjusted for time visit and for the basal value of the dependent variable. Treatment effect by center is reported when the interaction term is statistically significant.

**Palliative care Outcome Scale-Symptoms-Multiple Sclerosis (POS-S-MS) score – primary outcome**

Covariate	Coefficient (95% CI)	P value
HPA (vs. UC)	-2.10 (-4.18 – -0.03)	<b>0.047</b>
Rome (vs. Milan)	1.04 (-1.45 – 3.52)	0.41
Catania (vs. Milan)	0.82 (-1.58 – 3.21)	0.50
Age (years)	0.12 ( 0.01 – 0.22)	<b>0.026</b>
Severe cognitive compromise	3.54 ( 0.83 – 6.26)	<b>0.010</b>
Intervention group x center	–	0.62

**Schedule for the Evaluation of Individual Quality of Life-Direct Weighting (SEIQoL-DW) index – primary outcome**

Covariate	Coefficient (95% CI)	P value
HPA (vs. UC)	-2.49 (-11.15 – 6.17)	0.57
Rome (vs. Milan)	-3.82 (-15.09 – 7.45)	0.51
Catania (vs. Milan)	4.58 (-5.97 – 15.13)	0.39
Age (years)	-0.11 (-0.55 – 0.33)	0.62
EDSS score at baseline	-7.11 (-19.00 – 4.78)	0.24
Intervention group x center	–	0.70

**Palliative care Outcome Scale (POS) score**

Covariate	Coefficient (95% CI)	P value
HPA (vs. UC)	-1.18 (-3.11 – 0.76)	0.23
Rome (vs. Milan)	1.29 (-1.12 – 3.70)	0.29
Catania (vs. Milan)	4.74 ( 2.43 – 7.03)	<b>&lt; 0.001</b>
Age (years)	0.08 (-0.02 – 0.19)	0.12
Severe cognitive compromise	3.86 ( 1.41 – 6.32)	<b>0.002</b>
Intervention group x center	–	0.70

**Hospital Anxiety and Depression Scale (HADS) Anxiety score**

Covariate	Coefficient (95% CI)	P value
HPA (vs. UC)	0.52 (-0.93 – 1.98)	0.48
Rome (vs. Milan)	1.23 (-0.62 – 3.08)	0.19
Catania (vs. Milan)	3.46 ( 1.69 – 5.24)	<b>&lt; 0.001</b>
Age (years)	0.03 (-0.04 – 0.10)	0.46
EDSS score at baseline	-0.41 (-2.41 – 1.59)	0.69
Intervention group x center	–	0.24

**Hospital Anxiety and Depression Scale (HADS) Depression score**

<b>Covariate</b>	<b>Coefficient (95% CI)</b>	<b>P value</b>
HPA (vs. UC)	0.72 (-0.55 – 1.99)	0.26
Rome (vs. Milan)	-0.29 (-2.04 – 1.45)	0.74
Catania (vs. Milan)	2.48 ( 0.95 – 4.01)	<b>0.001</b>
Age (years)	0.08 ( 0.01 – 0.15)	<b>0.02</b>
EDSS score at baseline	2.34 (-0.51 – 4.19)	<b>0.01</b>
Intervention group x center	–	<b>0.02</b>
HPA (vs. UC) in Milan	2.13 (-0.01 – 4.27)	<b>0.05</b>
in Rome	1.97 (-0.17 – 4.12)	0.07
in Catania	-1.39 (-3.31 – 0.52)	0.15

**Functional Independence Measure (FIM) total score**

<b>Covariate</b>	<b>Coefficient (95% CI)</b>	<b>P value</b>
HPA (vs. UC)	-0.05 (-0.75 – 0.64)	0.88
Rome (vs. Milan)	0.26 (-0.64 – 1.15)	0.57
Catania (vs. Milan)	0.15 (-0.65 – 0.94)	0.71
Age (years)	-0.03 (-0.07 – 0.00)	0.06
Severe cognitive compromise	0.23 (-0.87 – 1.34)	0.68
Intervention group x center	–	0.56

**Zarit Burden Interview (ZBI) score**

<b>Covariate</b>	<b>Coefficient (95% CI)</b>	<b>P value</b>
HPA (vs. UC)	-0.41 (-4.30 – 3.48)	0.83
Rome (vs. Milan)	0.76 (-3.74 – 5.25)	0.74
Catania (vs. Milan)	-1.27 (-5.86 – 3.31)	0.58
Patient age (years)	0.09 (-0.11 – 0.30)	0.38
Patient with severe cognitive compromise	-2.10 (-6.92 – 2.72)	0.39
Carer age (years)	0.00 (-0.14 – 0.15)	0.95
Female carer	-2.93 (-7.41 – 1.53)	0.19
Living with the patient	0.38 (-5.84 – 6.61)	0.90
Intervention group x center	–	0.20

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**Table 4.** The 22 serious adverse events (20 patients) listed by report date (day/month/year). All were emergency ward admissions except the event of patient code 0318 (home death).

Patient code	Group	Baseline EDSS	Randomization date	Report date	Event Date	Weeks from randomization	Event description	Outcome
0315	HPA	9.0	08/04/15	11/05/15	05/05/15	4	Ab-ingestis pneumonia	Resolved (discharged)
0311	UC	8.5	07/03/15	18/05/15	06/04/15	4	Generalized anxiety	Resolved (discharged)
0211	HPA	8.0	13/05/15	26/05/15	23/05/15	1	Cardiac failure	Death (13 days H)
0314	HPA	8.5	22/03/15	27/05/15	11/05/15	7	Acute respiratory failure	Death (emergency ward)
0112	UC	9.5	23/03/15	28/05/15	12/05/15	7	Breathing difficulty	Resolved (21 days H)
0203	UC	8.5	03/03/15	03/06/15	27/05/15	12	Urine retention	Resolved (6 days H)
0111	HPA	9.0	17/03/15	16/06/15	08/05/15	7	Anarthria	Resolved (3 days H)
0305	UC	8.5	24/02/15	29/06/15	11/06/15	15	Contact dermatitis	Resolved (7 days H)
0321	UC	9.5	30/05/15	20/07/15	10/07/15	5	Dysphagia	Gastrostomy tube placement (3 days H)
0308	HPA	8.0	14/03/25	12/08/15	07/08/15	21	Breathing difficulty, vomiting	Resolved (1 day H)
0318	HPA	8.5	02/05/15	12/08/15	07/08/15	14	Cardiac failure	Death (home)
0203	UC	8.5	03/03/15	04/09/15	30/08/15	26	Bladder catheter malfunctioning	Resolved (discharged)
0213	HPA	9.0	04/06/15	14/10/15	29/09/15	16	Fever, breathing difficulty	Resolved (discharged)
0322	HPA	9.0	30/05/15	09/10/15	02/09/15	13	Acute urine retention/infection	Resolved (discharged)
0218	HPA	8.5	30/07/15	07/01/16	26/12/15	21	Arrhythmia	Resolved (3 days H)
0328	HPA	8.5	25/07/15	16/01/16	22/12/15	22	Necrotizing fasciitis	Day surgery (discharged)
0136	UC	8.0	28/10/15	20/01/16	11/12/15	6	Traumatic wound	Resolved (wound suture)
0220	HPA	9.0	02/10/15	13/02/16	23/01/16	16	Fever, macrohematuria	Resolved (1 day H)
0137	HPA	8.0	06/11/15	04/03/16	23/02/16	15	Difficulty with bladder catheter removal	Resolved (discharged)
0138	HPA	8.5	18/11/15	21/03/16	19/02/16	13	Acute urine retention, constipation	Resolved (discharged)
					22/02/16	13	Acute urine retention, abdominalgya	Resolved (discharged)
					01/03/16	15	Fever, bronchitis, macrohematuria	Resolved (1 day H)

EDSS, Expanded Disability Status Scale; H, hospitalization; HPA, home palliative approach; UC, usual care.

**Figure legends**

**Figure 1.** CONSORT 2010 Flow diagram of the trial. HPA is home palliative approach, UC is usual care.

**Figure 2.** The care needs addressed (dark grey, overall n=338) and fulfilled (light grey, n=276) as reported by the home palliative approach (HPA) teams. Care needs are grouped into 11 pre-set categories and three domains [16].

**Figure 3.** Change in the two primary outcome measures Palliative care Outcome Measure-Symptoms-Multiple Sclerosis (POS-S-MS) and Schedule for the Evaluation of Individual Quality of Life-Direct Weighting (SEIQoL-DW) by intervention group (intention to treat data). CI is confidence interval, HPA is home palliative approach, UC is usual care.

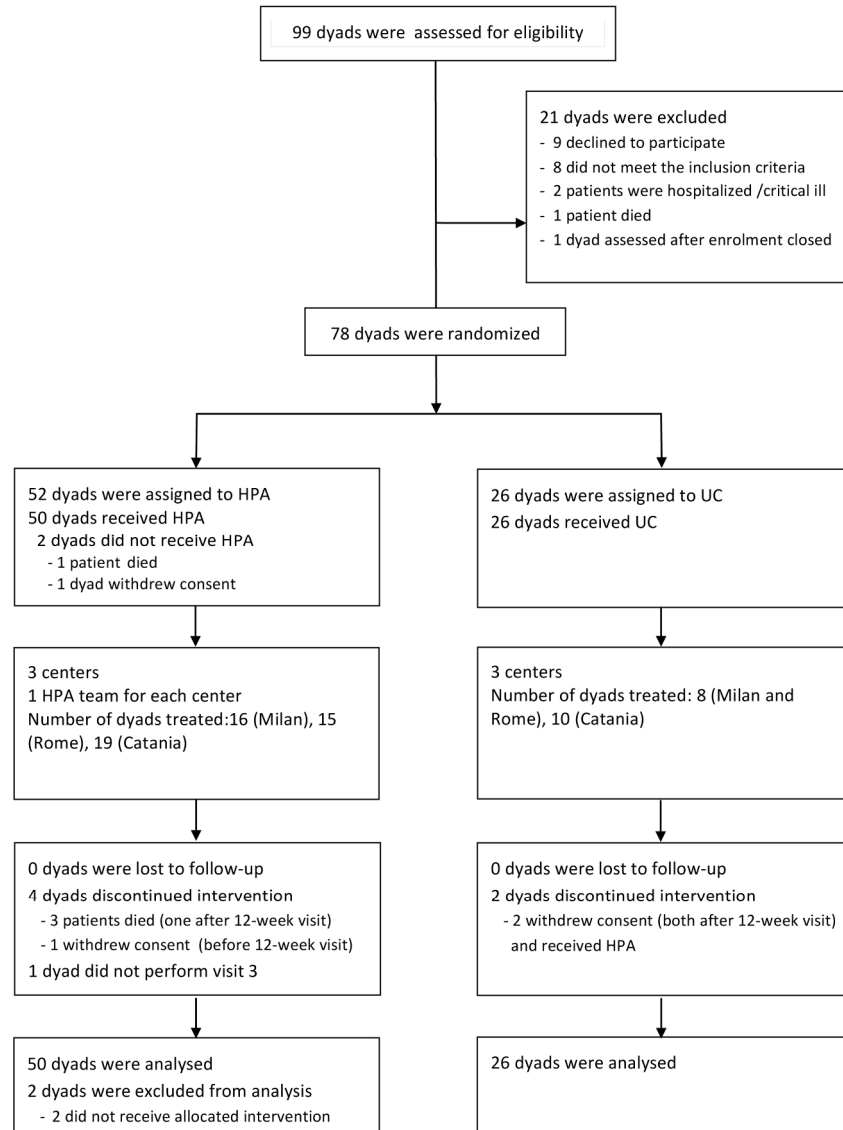


Figure 1. CONSORT 2010 Flow diagram of the trial. HPA is home palliative approach, UC is usual care.

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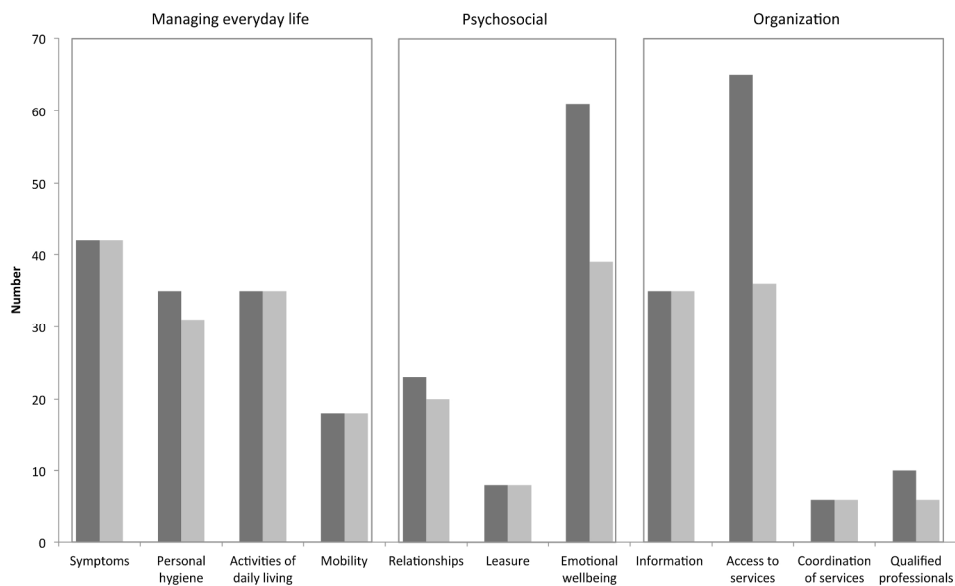


Figure 2. The care needs addressed (dark grey, overall n=338) and fulfilled (light grey, n=276) as reported by the home palliative approach (HPA) teams. Care needs are grouped into 11 pre-set categories and three domains [16].

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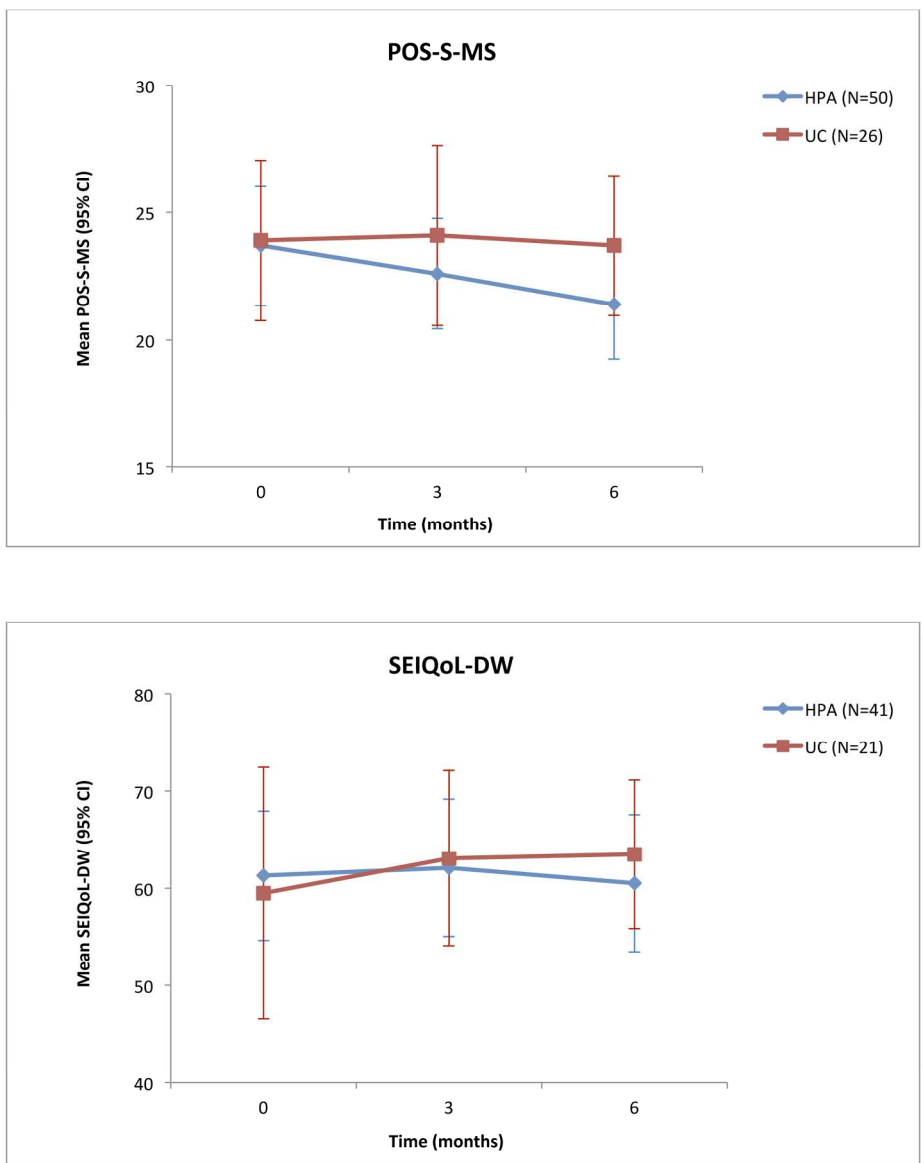
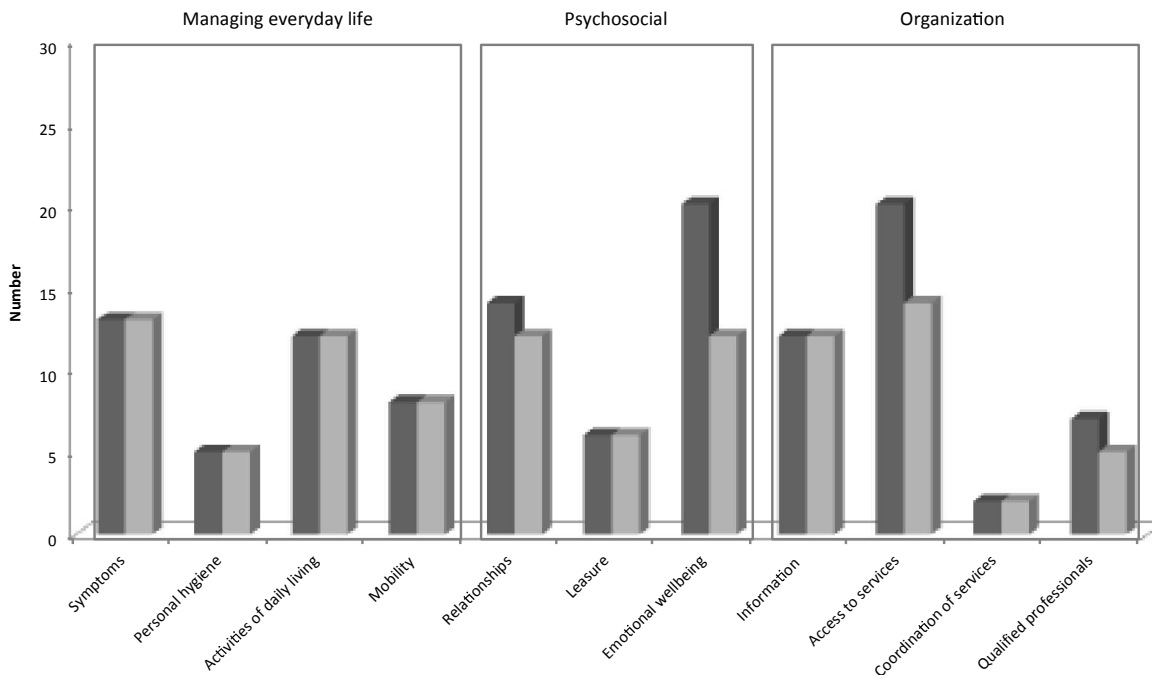


Figure 3. Change in the two primary outcome measures Palliative care Outcome Measure-Symptoms-Multiple Sclerosis (POS-S-MS) and Schedule for the Evaluation of Individual Quality of Life-Direct Weighting (SEIQoL-DW) by intervention group (intention to treat data). CI is confidence interval, HPA is home palliative approach, UC is usual care.

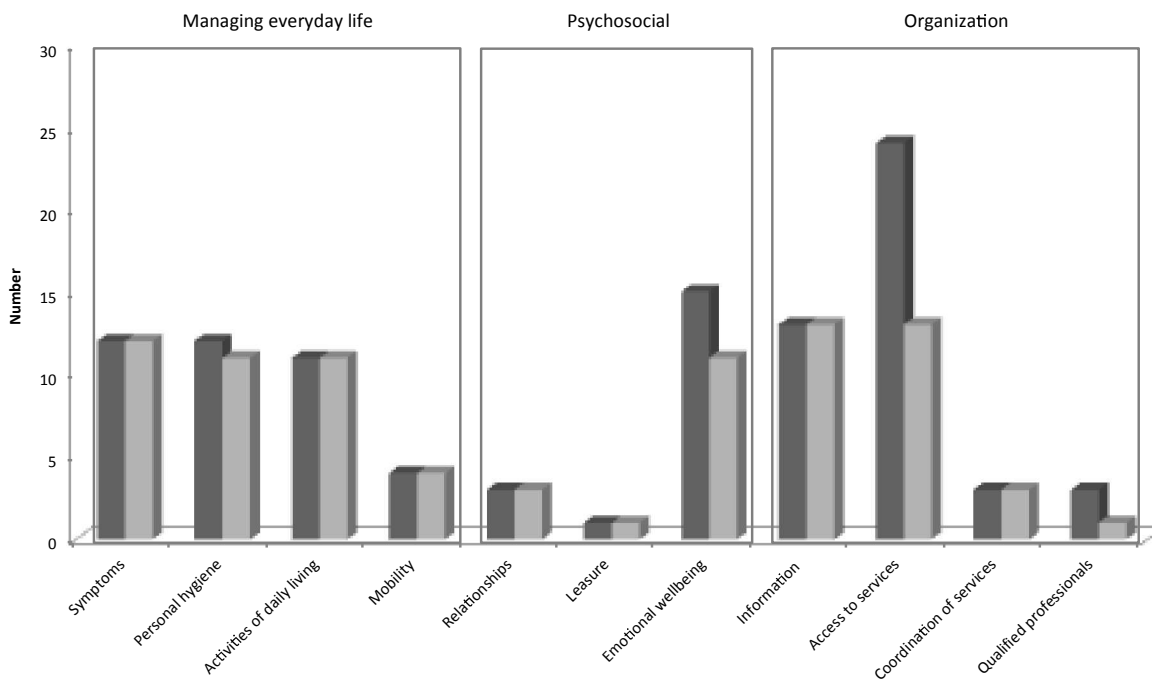
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**Supplementary figure.** The care needs addressed (dark grey, Milan n=119; Rome n=101; Catania n=119) and fulfilled (light grey, Milan n=101; Rome n=83; Catania n=92) as reported by the home palliative approach (HPA) teams. Care needs are grouped into 11 pre-set categories and three domains [16].

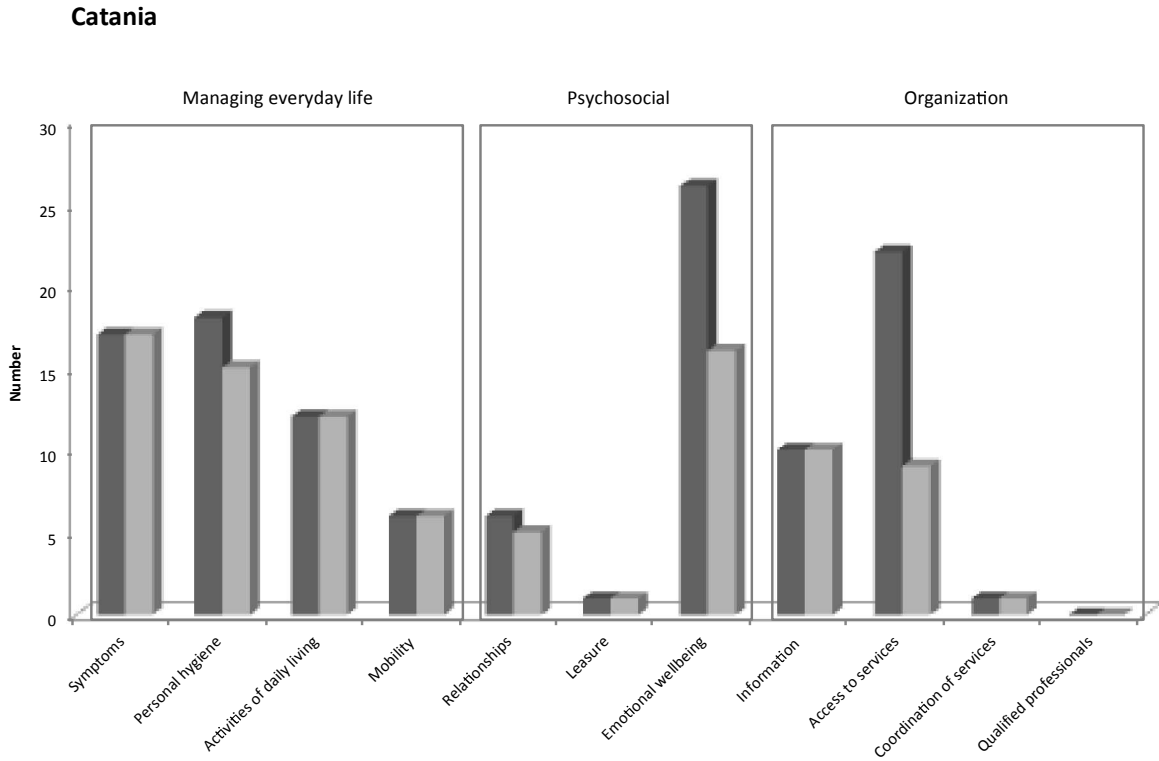
**Milan**



**Rome**



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Peer Review

**Supplementary table 1.** Generalized linear models (per protocol analysis) of patient outcomes. EDSS is Expanded Disability Status Scale, HPA is home palliative approach, UC is usual care. All estimates are adjusted for time visit and for the basal value of the dependent variable. Treatment effect by center is reported when the interaction term is statistically significant.

#### Palliative care Outcome scale-Symptoms-Multiple Sclerosis (POS-S-MS) score – primary outcome

Covariate	Coefficient (95% CI)	P value
HPA (vs. UC)	-1.94 (-3.98 – 0.09)	0.062
Rome (vs. Milan)	1.40 (-1.09 – 3.89)	0.27
Catania (vs. Milan)	0.86 (-1.47 – 3.20)	0.47
Age (years)	0.13 ( 0.02 – 0.24)	<b>0.014</b>
Severe cognitive compromise	3.56 ( 0.92 – 6.20)	<b>0.008</b>
Intervention group x center	–	0.74

#### Schedule for the Evaluation of Individual Quality of Life-Direct Weighting (SEIQoL-DW) index – primary outcome

Covariate	Coefficient (95% CI)	P value
HPA (vs. UC)	-2.26 (-10.98 – 6.44)	0.61
Rome (vs. Milan)	-5.56 (-17.49 – 6.37)	0.36
Catania (vs. Milan)	3.19 ( -7.57 – 13.95)	0.56
Age (years)	-0.17 ( -0.65 – 0.29)	0.46
EDSS score at baseline	-5.81 (-18.28 – 6.66)	0.36
Intervention group x center	–	0.71

#### Palliative care Outcome Sale (POS) score

Covariate	Coefficient (95% CI)	P value
HPA (vs. UC)	-1.23 (-3.16 – 0.69)	0.21
Rome (vs. Milan)	1.06 (-1.27 – 3.41)	0.37
Catania (vs. Milan)	4.65 ( 2.38 – 6.92)	<b>&lt; 0.001</b>
Age (years)	0.08 (-0.02 – 0.17)	0.11
Severe cognitive compromise	3.87 ( 1.47 – 6.28)	<b>0.002</b>
Intervention group x center	–	0.62

#### Hospital Anxiety and Depression (HADS) Anxiety score

Covariate	Coefficient (95% CI)	P value
HPA (vs. UC)	0.56 (-0.93 – 2.06)	0.46
Rome (vs. Milan)	1.39 (-0.61 – 3.39)	0.17
Catania (vs. Milan)	3.54 ( 1.67 – 5.41)	<b>&lt;0.001</b>
Age (years)	0.03 (-0.04 – 0.11)	0.40
EDSS at baseline	-0.55 (-2.68 – 1.56)	0.60
Intervention group x center	–	0.27

**Hospital Anxiety and Depression (HADS) Depression score**

<b>Covariate</b>	<b>Coefficient (95% CI)</b>	<b>P value</b>
HPA (vs. UC)	0.68 (-0.60 – 1.96)	0.29
Rome (vs. Milan)	-0.56 (-2.28 – 1.16)	0.52
Catania (vs. Milan)	2.42 ( 0.84 – 4.01)	<b>0.003</b>
Age (years)	0.08 ( 0.01 – 0.15)	<b>0.02</b>
EDSS score at baseline	2.58 ( 0.32 – 0.63)	<b>0.01</b>
Intervention group x center	–	<b>0.02</b>
HPA (vs. UC) in Milan	2.19 ( 0.06 – 4.34)	<b>0.04</b>
in Rome	1.83 (-0.03 – 3.97)	0.09
in Catania	-1.41 (-3.33 – 0.50)	<b>0.01</b>

**Functional Independence Measure (FIM) total score**

<b>Covariate</b>	<b>Coefficient (95% CI)</b>	<b>P value</b>
HPA (vs. UC)	-0.10 (-0.84 – 0.63)	0.77
Rome (vs. Milan)	0.26 (-0.65 – 1.18)	0.57
Catania (vs. Milan)	0.01 (-0.81 – 0.85)	0.96
Age (years)	-0.04 (-0.08 – -0.00)	<b>0.02</b>
Severe cognitive compromise	0.29 (-0.89 – 1.47)	0.63
Intervention group x center	–	0.57

**Supplementary table 2.** Generalized linear models (per protocol analysis) of carer's Zarit Burden Interview (ZBI), Hospital Anxiety and Depression Scale (HADS), and SF-36 composite scores. HPA is home palliative approach, UC is usual care. All estimates are adjusted for time visit and for the basal value of the dependent variable. Treatment effect by center is reported when the interaction term is statistically significant.

**ZBI score**

<b>Covariate</b>	<b>Coefficient (95% CI)</b>	<b>P value</b>
HPA (vs. UC)	-0.44 (-4.29 – 3.40)	0.82
Rome (vs. Milan)	0.84 (-3.88 – 5.57)	0.72
Catania (vs. Milan)	-1.78 (-6.41 – 2.84)	0.45
Patient age (years)	0.04 (-0.16 – 0.25)	0.66
Patient with severe cognitive compromise	-2.40 (-7.17 – 2.37)	0.32
Carer age (years)	-0.19 (-0.17 – 0.13)	0.80
Female carer	-2.23 (-6.20 – 1.72)	0.26
Living with the patient	0.92 (-5.13 – 6.97)	0.76
Intervention group x center	–	0.14

**HADS Anxiety score**

<b>Covariate</b>	<b>Coefficient (95% CI)</b>	<b>P value</b>
HPA (vs. UC)	0.43 (-0.84 – 1.69)	0.50
Rome (vs. Milan)	-0.31 (-1.85 – 1.21)	0.68
Catania (vs. Milan)	-0.20 (-1.74 – 1.34)	0.79
Patient age (years)	0.01 (-0.05 – 0.07)	0.75
Patient with severe cognitive compromise	-0.88 (-2.47 – 0.70)	0.27
Carer age (years)	0.03 (-0.01 – 0.08)	0.20
Female carer	2.06 ( 0.73 – 3.39)	<b>0.002</b>
Living with the patient	-0.65 (-2.60 – 1.29)	0.51
Intervention group x center	–	0.62

**HADS Depression score**

<b>Covariate</b>	<b>Coefficient (95% CI)</b>	<b>P value</b>
HPA (vs. UC)	0.49 (-0.78 – 1.77)	0.45
Rome (vs. Milan)	-0.25 (-1.82 – 1.32)	0.75
Catania (vs. Milan)	0.32 (-1.24 – 1.88)	0.68
Patient age (years)	0.02 (-0.04 – 0.08)	0.53
Patient with severe cognitive compromise	-0.03 (-1.65 – 1.58)	0.96
Carer age (years)	0.07 ( 0.02 – 0.12)	<b>0.003</b>
Female carer	1.34 ( 0.01 – 2.67)	<b>0.047</b>
Living with the patient	0.25 (-1.79 – 2.30)	0.80
Intervention group x center	–	0.37

## SF-36 Physical Composite score

Covariate	Coefficient (95% CI)	P value
HPA (vs. UC)	-0.21 (-2.88 – 2.44)	0.87
Rome (vs. Milan)	3.43 ( 0.11 – 6.75)	<b>0.04</b>
Catania (vs. Milan)	1.95 (-1.27 – 5.17)	0.23
Patient age (years)	-0.01 (-0.12 – 0.15)	0.82
Patient with severe cognitive compromise	-0.09 (-3.27 – 3.08)	0.95
Carer age (years)	-0.07 (-0.18 – 0.03)	0.16
Female carer	0.51 (-2.24 – 3.26)	0.71
Living with the patient	0.12 (-3.87 – 4.12)	0.95
Intervention group x center	–	0.26

## SF-36 Mental Composite score

Covariate	Coefficient (95% CI)	P value
HPA (vs. UC)	0.09 (-3.63 – 3.81)	0.96
Rome (vs. Milan)	-0.75 (-5.29 – 3.79)	0.74
Catania (vs. Milan)	-3.60 (-8.04 – 0.84)	0.11
Patient age (years)	-0.02 (-0.21 – 0.16)	0.82
Patient with severe cognitive compromise	-2.85 (-7.21 – 1.51)	0.20
Carer age (years)	-0.06 (-0.19 – 0.07)	0.39
Female carer	1.39 (-2.47 – 5.25)	0.48
Living with the patient	0.04 (-5.51 – 5.59)	0.98
Intervention group x center	–	<b>0.04</b>
HPA (vs. UC) in Milan	-6.73 (-13.30 – -0.16)	<b>0.04</b>
in Rome	1.87 ( -4.55 – 8.31)	0.56
in Catania	3.51 ( -2.18 – 9.21)	0.22

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**Supplementary box.** Main challenges to intervention delivery identified (thematic analysis) in the HPA team focus group meeting conducted at the end of the trial. The five themes were: (1) the indirect role of the teams (according to the trial protocol); (2) the limited availability/responsiveness of the local services; (3) a general submission and difficulty of the dyads to express their needs; 4) team working issues, particularly those pertaining to newly-formed teams, acting at patient home; 5) emotional involvement.

### 1. Indirect role of the teams

*"It's an additional burden to them [the dyads] and also a reason of frustration because they still seek support, they seek help, but then in fact, apart from mediating the relationships with the local health providers, the offices and so on, we couldn't do anything else."* [Psychologist, Rome team]

*"It was clear that our role was not of direct care, it was a facilitating role, therefore, to say the representation was clear, the problem was how to do that in practice, how to accomplish..."* [Psychologist, Milan team]

*"I had a difficult time understanding what to do, what I could and it was really right to do according to the study objectives"* [Neurologist, Milan team]

### 2. Limited availability/responsiveness of the local services

*"One can be a facilitator when services are in place, but when no services are available what do I facilitate? In Rome, for example, so many of them do not make rehabilitation at the centers anymore, as they have difficulty getting around, ambulances cost so much, etc."* [Psychologist, Roma team]

*"You have difficulty in contacting the GP, and when you finally make it, he says: "well, there you are, one more reason not to involve me"; that is to say, they're good professionals, but obviously in this system they have a hard time, such a hard time..."* [Nurse, Milan team]

*"[Neurologists] know nothing of what has happened, they have not heard from them, not viewed them, so it's tricky to involve them, inform them, make them participate to what you're doing at home"* [Psychologist, Roma team]

*"I have a little informed them, I sent them emails where I made a summary of the study practically, and then to each doctor we sent our relations, the social, the psychological, the nurse and medical relation. But no answer..."* [Nurse, Catania team]

### 3. Difficulty of the dyads to express their needs

*"In these countless years of illness [patients and informal carers] got accustomed to not having the services, to not receiving, to have bureaucratic problems, whenever they need to solve a problem they must still make some laps, then, they were not expecting great things from us"* [Nurse, Rome team]

*"We received many expressed questions but a great deal of unspoken questions: they came out, that is, they asked for help on issues that apparently were organizational, but in fact were about conflicts between family members that had deteriorated, impacting on patient care and organization... These occurrences were crucial and taxing for us, as by recognizing these unexpressed questions, it was up to us figuring whether, how and when there were intervention areas, or not."* [Social worker, Catania team]



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"What impressed me most was the difficulty for the dyads to try to explore their needs, as if they were not used to doing this. I guess the first time they really approached this was when they performed the baseline visit ... For the relatives it was too difficult to express their personal needs, as all their needs were linked in some way to the needs of the patient... this required time and work." [Psychologist, Milan team]

"... and for years [problems] are kept there, you have no access, they too have no access, so even if you become aware because of some dynamics that there are problems, they [the dyads] do not acknowledge this." [Psychologist, Rome team]

"There were also unmet needs regarding the treatment of certain symptoms. Pain is one of the symptoms that most of them have, but they've got used to it, they talk about pain as something normal, so I imagine other important physical problems they live with for such a long time." [Nurse, Rome team]

#### 4. Team working issues

"To me, yielding ground to the other colleagues when meeting the expectations of the patient was hard, perhaps because most needs were about medical issues." [Neurologist, Catania team]

"Working as a team, as a group, was a bit difficult, I'm not sure whether we as a group needed more training or whether this need was more general, and regarded how to manage those dynamics that usually manifest within a group." [Social worker, Catania team]

"Team members had specific competences, but some like me lacked skills on the care of MS patients, so I had to gain knowledge on a new disease... this was added to the need to become familiar with the other team members." [Nurse, Rome team]

#### 5. Emotional involvement

"In spite of the fact that we're fairly seasoned professionals, the emotional load and involvement were remarkable. Getting into patient houses and finding relationship difficulties, psychological conflicts... an enormous emotional burden which willy-nilly we have in part taken charge of." [Social Worker, Catania team]

"And then at the end there was a sense of frustration over what you actually can do... All in all, you can only say: the study ends, they are still there with their mess..." [Nurse, Milan team]