Economic evaluation of an integrative psychotherapeutic nursing home programme to reduce multiple psychiatric symptoms of psychogeriatric patients and caregiver burden; A randomized controlled trial¹)

¹) Hakkaart-van Roijen L, Bakker TJEM, Al MJ, van der Lee J, Duivenvoorden H, Ribbe MW, Huijsman R,
1. **Introduction**

In psychogeriatric patients who suffer from cognitive impairment or dementia, there is an 80% prevalence of two or more psychiatric symptoms, e.g. depression, anxiety, paranoia, aggression. 1–5 Multiple psychiatric symptoms (MPS) have many related negative secondary effects. For the patients there are negative effects on cognitive functioning, quality of life and they predict admission to a nursing home. Furthermore, MPS are a burden for the caregiver. 3, 6–12 Moreover, these MPS are number one among the top three problems experienced by dementia patients and their caregivers. 13 In usual nursing home care, psychotropic drugs are widely used to treat the MPS of psychogeriatric patients despite of their limited effects and potentially harmful side-effects e.g. (a)typical antipsychotics. 2, 5, 14, 15 There is a lack of integrative psychotherapeutic programmes, even though reports in the literature indicate that for individual psychiatric symptoms, e.g. depression and anxiety, as well as caregiver burden, psychotherapeutic treatment may be effective in both nursing home and primary care settings. 16–19, 20–24 However, psychotherapeutic interventions focusing on the MPS of psychogeriatric patients who suffer from cognitive impairment or dementia are complex, due to their multiplicity in combination with cognitive disorders, somatic co-morbidity, and social problems (e.g. relationships, loneliness) 25, 26. Furthermore, integrative psychotherapeutic programmes in nursing homes have never been evaluated in large-scale comprehensive studies. 10, 16, 27–30 For these reasons, we developed a unique integrative psychotherapeutic nursing home programme: integrative reactivation and rehabilitation (IRR). 31 The performed RCT was designed to test the effectiveness of IRR to reduce MPS in psychogeriatric patients who suffer from cognitive impairment or dementia, and burden of the caregiver. The primary analyses regarded the mean differences between IRR and the control group (usual care) on continuous data of the primary and secondary outcome variables. The results of this analysis are published elsewhere. 32

From the perspective of the caregivers, the IRR had a significant and moderate to large surplus effect (up to 34%) in reducing the MPS of psychogeriatric patients who suffer from cognitive impairment of dementia in both short term and the long term. In fact, at the six-month follow-up there was a total reduction in MPS up to 46% in number and 61% in severity. Furthermore, with regard to secondary outcome variables, on caregiver burden and competence the IRR had a large positive surplus effect (up to 36%) at the end of the treatment. During the follow-up the surplus effect even increased to a reduction of 50%, while usual care had hardly any effect at all. Irrespective of beneficial clinical effects it is important to take into account the economic aspects, i.e. an economic evaluation. 33–36 In this paper we report the results of an economic evaluation of a RCT in which IRR was compared to usual multidisciplinary nursing home care. The two objectives of this economic evaluation were to assess the cost-utility of IRR as well as the cost-effectiveness on six outcome variables of IRR compared to usual care (UC).
2. Materials and methods

2.1 Patients

The psychogeriatric patients were recruited from the urban region of Nieuwe Waterweg Noord (NWN), near Rotterdam in the Netherlands (approximately 180,000 inhabitants). The patients were referred from an (ambulant) mental health service (5.4%), a general hospital (13.8%), a memory clinic (6%) and general practitioners or primary healthcare services (75.1%). Before inclusion, all referred patients underwent a comprehensive geriatric assessment. The initial inclusion criteria were a DSM IV classification of dementia, amnestic disorders or other cognitive disorders. Additional inclusion criteria were: 1) age: ≥65 years; 2) cognitive functioning: MMSE ≥8 and ≤27 as well as Barthel Index (BI) ≥5 and ≤19; 3) psychiatric symptoms: Neuropsychiatric Inventory (NPI) 3 or more symptoms, and 4) informed consent. The exclusion criteria were: 1) delirium; 2) life-threatening somatic co-morbidity; 3) active coercive admission regime (according to psychiatric legislation), and 4) insufficient command of the Dutch language.

2.2 Design

The economic evaluation was embedded in an open RCT, with a parallel group design and which was performed from 2001 until 2006. The patients who met the selection criteria, were asked to participate in the RCT. If the participant or his caregiver signed a written informed consent, he was randomly assigned to either IRR (experimental intervention) or usual care (UC). By the inclusion committee randomization was carried out block wise (i.e. three subjects per block.) In the first half of the study the patients were assigned in a ratio 1 (IRR): 2 (UC). Due to limited numbers of eligible patients and time restrictions of the study, in the second half the assignment ratio was reversed to 2 (IRR): 1 (UC). In total, the study included 168 patients, 81 assigned to IRR and 87 to UC (1). In the original study, ‘multiple psychiatric symptoms of the patient’ was the primary outcome variable for effectiveness. In view of clinically relevant background information of the effect of IRR, ‘Burden’ of the caregiver, ‘Cognitive functioning’ and ‘Quality of life’ of the patient were selected as secondary outcome variables. For economic evaluation the data of direct medical costs of the patient were collected. The outcome variables were simultaneously assessed in both arms at two moments: T1 (within two weeks after intake) and T3 (follow-up; six months after the end of intervention), but measurements of the costs were conducted every 8 weeks from the moment of inclusion (TO) over the preceding last four weeks. Blinding of the two trained co-workers collecting the outcome variables was not feasible as they had to visit the patients as well as their caregivers and knew their intervention history. This study was approved by the Medical Ethical Committee of the Erasmus University Medical Centre.
2.3 Intervention

The IRR programme had a duration of 13 weeks with clinical admission to a separate 15-bed specialized unit of a psychiatric skilled nursing home. In addition to usual multidisciplinary nursing home care, including psychotropic drugs treatment, the IRR consisted of integrative psychotherapeutic interventions for MPS of the psychogeriatric patient and family therapy for the caregiver. The psychotherapeutic interventions were based on a problem solving theoretical framework. A more extensive description of IRR programme has been published elsewhere.

Usual care (UC) consisted of a relatively high level of multidisciplinary nursing home care provided in the following settings: at home (25.3%), at home with mental healthcare (out-reaching) or psycho-geriatric day care/treatment (15.7%), in a home of assisted living (7.2%) and in a nursing home (51.8%).

The UC was provided by different types of core multidisciplinary teams, each with a different theoretical framework, mostly emotion-oriented.

2.4 Assessments

To answer the two objectives of the economic evaluation we have used two sets of instruments. One for the patient and caregiver and one for the economic aspects. For the patient and caregiver we used the following instruments out of a larger set of assessments. MPS of the patient (the primary outcome variable) was assessed by means of the Neuropsychiatric Inventory (NPI 12 item version: ‘NPI-sum-severity’: 0 to 144; 0 = no severity symptoms at all). NPI was administrated to the caregiver. Of the secondary outcome variables, General burden of the caregiver was assessed with Caregiver Burden (CB: 0 to 100; 0 = optimal) and Caregiver Competence List (CCL: 28 to 112; 112 = optimal) assessed the competence of the caregiver. For Cognitive functioning of the patient, memory was measured by the Mini Mental State Examination (MMSE: 0 to 30; 30 = normal) and self care by Barthel Index (BI: 0 to 20; 20 = normal). To assess the risk for being placed in a nursing home the Global Deterioration Scale (GDS: 1-7; 1 is normal) was used. For somatic comorbidity ICD-10 was used. Furthermore, the DSM IV disorders (axes I and II) were classified by a research psychiatrist. Finally, the following demographic data were collected from patient and caregiver: gender, age, marital status, family relation, domicile, education level, income level and job employment.

For the economic evaluation (CUA) we used the following instruments. Quality of life was assessed with EQ5D (–0.59 to 1.0; 1.0 = optimal) completed by the patient. The EQ5D is a validated tool for measuring general health–related quality of life. EQ5D consists of five items (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each having the rating of ‘no problems’, ‘some problems’ and ‘extreme problems’. The health descriptions can be linked directly to empirical valuations of the general public, which allows utilities to be computed. We used TiC-P to collect data on direct medical costs from the patients. The TiC-P measures medical resource utilisation by asking the number of contacts over the
Economic evaluation of IRR preceding last four weeks with different (medical and psychological) health care providers e.g. general practitioner, psychiatrist, medical specialist, physiotherapist, day care/hospital and nursing home length of stay. The number of days admitted to the nursing home was collected directly from the participating centres. Unit prices for all nursing home days were estimated based on information of the financial department of Argos Zorggroep. Data on the direct (e.g. medical staff, nursing staff) and indirect costs (e.g. overhead, housing) of 2004 was used to calculate the unit costs per day for IRR and UC. Other health care utilisation was valued by the reference unit prices. Unit prices of health care services for 2004 were adjusted to prices of 2005 by using the consumer price index (www.cbs.nl). Subsequently, the number of medical contacts was multiplied by the corresponding unit costs to estimate the costs. All costs were estimated for the year 2005 and are presented in Euros. The patient mean utility scores were estimated by applying the area-under-the-curve method (AUC), which is implemented by summing the areas of the geometrical shapes obtained by linearly interpolating between utility scores over the study period. The costs and utility scores of patients who died were valued zero if one died in the first 4 weeks of a measurement period and in the consecutive measurement periods. If a patient died in the last 4 weeks of a measurement period we valued the costs and utility scores as missing or the available costs of the measurement period in which the person died, and zero in the consecutive periods.

2.5 Statistical analyses

The economic evaluation was based on all relevant costs due to medical resource utilisation by the patients (direct medical costs). The direct medical costs of caregivers were not available. In order to account statistically for missingness, we used in the cost-utility analysis the technique of multiple imputation. This is a technique in which each missing value is replaced by m>1 simulated values. After the multiple imputations are generated, the m versions of the complete data were individually analysed by standard statistical methods for complete data. Subsequently, the results of the m analyses were combined including the uncertainty as a result of missing data. For the proportions of missing information in the current study, m=10 was found to be sufficiently large to stabilise the outcomes in terms of the standard errors for all analyses. The overall mean costs are calculated as the mean of the mean costs in each dataset. The overall associated variance is found by combining the variance within the datasets with the variance between the datasets. We used the Monte Carlo Markov Chain (MCMC) approach to impute the missing values. This MCMC approach assumes the underlying distribution to be multivariate normal, although it was shown in a large simulation study that even with skewed data this approach often performs well. Multiple imputation gives valid results if data are missing completely at random (MCAR), and if data are at random (MAR). MAR assumes that missingness de-
pends only on observed variables. The cost-utility was evaluated by relating the difference in direct medical costs per patient receiving either IRR or UC to the difference in terms of Quality Adjusted Life Years gained (QALY), which yielded a cost per QALY estimate. The endpoint of the cost utility analysis was 40 weeks. In addition, to estimate cost-effectiveness of IRR we tested the mean differences between the two interventions (i.e. IRR and UC) on the primary outcome variable (NPI), on four selected secondary clinical outcome variables and on the EQ5D. We used a complete cases (CC) approach, excluding patients who had missing data before the endpoint. Specifically, in case of a relatively high number of drop outs in both arms of the study and no significant differences between drop outs on relevant baseline and outcome measures or on time participating in the programme, results of a CC analysis may present a more accurate estimation of the clinical effect of IRR. The very reason is that only patients and caregivers who fully participated in IRR programme, could completely benefit of the offered interventions. The cost-effectiveness analysis spanned an interval from the start of intervention (Ti) until the endpoint at 40 weeks. We compared differences in total medical costs combined with mean differences in effects in terms of Incremental Cost-Effectiveness Ratio (ICER). For estimation of the participation interval of dropouts (time in days participating in the study) a Cox-regression analysis was performed. The 95% confidence intervals (CI) were presented when relevant. All significance testing was fixed at P<0.05 (two-tailed). The data were analysed according to the intention to treat (ITT)-principle. The statistical analyses were performed with the software programmes SPSS, version 15, and SAS, version 8.2

3. Results

3.1 Characteristics of the study sample

The flow-chart (Figure 1) shows that of the 336 eligible 168 (50%) consented to participate in the RCT. The non-participants did not differ significantly from the participants on the inclusion criteria. The 168 patients were randomly assigned to either IRR (N = 81) or UC (N = 87). The differences between the two study groups in number of dropouts – the majority caused by death - were insignificant at all measurement points. Moreover, the dropouts did not differ significantly with regard to any baseline assessment or on length of time participating in the programme (Cox regression analysis: HR 1.21; P<0.54). With respect to biographical data there were no significant differences between the two groups (Table 1). Mean somatic co-morbidity in the IRR group was significantly higher (IRR 5.6; UC 4.5; P<0.01). A mean GDS-score 4.2 (sd 0.8) suggested that the study sample consisted of psychogeriatric patients with mild cognitive impairment or dementia who were at risk for permanent admission to a nursing home.
At T1 (Table 2) there were no significant mean differences between the IRR group and the UC group. Specifically, the mean sum-severity of NPI-symptoms of the patient (IRR 35.90 and UC 29.68) did not differ significantly.

3.2 Cost utility analysis

The results of the cost and QALY analyses are presented as mean values (including 95% CI). At baseline (week 8), data of TiC-P and EQ5D were available for 96% (n=161) of the subjects. At 40 weeks follow-up, these data were available for 38% (n=63) of the participants. Table 3 presents the results of mean costs per patient and mean QALY analysis after applying multiple imputation (MI). At 40 weeks the direct medical costs in IRR were significantly higher (€ 4,572,--) than those in UC (95% CI: 364.24 to 8797.76). This implies € 53,-- extra per IRR-treatment day (in total: on average 90 days treatment duration). At the same time the number of QALYs of the patients was non-significantly 0.02 lower in IRR (95% CI:-0.10 to 0.05).

3.3 Cost effectiveness analysis

In Table 4, the costs for the individual cost-factors, based on the CC approach, are presented. This table shows that the highest costs had to be ascribed to nursing home costs. The mean nursing home costs per patient (including the costs of IRR) after 40 weeks were non-significantly higher in IRR than in UC. However, the costs of home care and day care were significantly lower in IRR at 40 weeks. In Table 5 the cost-effectiveness after 40 weeks i.e. estimated ICER is presented. IRR was significantly more effective on the primary outcome variable NPI-sum-severity of the patient, and the secondary outcome variables caregiver burden and caregiver competence; on EQ5D of the patient the difference was non-significant. Regarding medical costs, for NPI-sum-severity of the patient, the net-result equalled to about € 320.--, implying that for one more point improvement on this outcome variable in IRR the costs were € 320.--) (mean difference 10 points). The least expensive was improvement on general burden of the caregiver, with almost € 130.-- for one point more improvement in IRR compared to UC (mean difference 25 points). Clearly more expensive was improving on competence of the caregiver in IRR compared to UC. The net-costs were € 540.-- (mean difference 6 points). The net-costs of improvement on EQ5D of the patient were high, namely about € 80,000.-- for one point improvement (mean difference 0.04 points). As IRR performed (non-significantly) less well on the other secondary outcome variables (MMSE and BI) than UC, it did not make sense to estimate their net-costs.
4. Discussion

The objective of this study was an economic evaluation of IRR on cost-utility as well as on cost-effectiveness. Therefore, the cost-utility (QALYs) and cost-effectiveness (ICERs) of IRR were estimated by comparing this intervention to usual care at six month follow-up after the end of intervention i.e. 40 weeks. The cost-utility analysis suggests the amount of QALYs for psychogeriatric patients did not differ significantly between IRR and Usual Care while the costs were significantly lower in UC. It has to be noted that the changes on the underlying EQ5D-scores (number and mean) were very small in both study groups. Looking at total medical costs, IRR was more expensive, if these estimations were statistically adjusted for dropout; about € 53.-- per day, for 90 days € 4.572.--. In contrast, the effectiveness analysis (ICERs) showed that significant improvement of patients and caregivers participating in IRR on general burden was least expensive; about € 130.-- per point. Improvement on severity of multiple psychiatric symptoms took a middle position with about € 540.-- per point. One point improvement on competence costed € 540.--. Improvement on EQ5D was non-significant higher in IRR, but was most expensive; about € 80,000.-- per point. The findings of the ICER are clinically relevant results because MPS of patients and caregiver burden are the two as most problematic experienced phenomena in dementia care. However, cost-effectiveness results can not be easily compared to cost-effectiveness results of other health care interventions, because there are no reference values of costs per effect unit for the different clinical outcome measures. Hence, this type of information (ICERs) is of less value in health care policy decision making than QALYs.

When we compared in a post-hoc analysis the costs of patients who improved on the primary outcome variable NPI-sum severity we found that in both groups the improved patients were significantly more cost-expensive than the non-improved. Improving seemed inextricably related to more medical costs. In IRR, significantly more patients improved and as a consequence they were responsible for most of the higher total medical costs in IRR (not presented). An explanation may be that improved patients lived longer. In a foregoing study we found that patients discharged after IRR at home or to a residential home with restricted support had a 3.2 time higher probability of survival than the patients who were discharged to a nursing home.59

Remarkable and problematic is the difference in results between QALYs and ICERs found in this study. The ICERs of clinically relevant outcomes i.e. severity of psychiatric symptoms of psychogeriatric patients, caregiver burden and competence were clearly in favour of IRR, with relatively large numbers of improved patients (≥ 0.5 sd). At the same time, the numbers needed to treat (NNT) for NPI of IRR were relatively low i.e. four. For comparison the NNT of donepezil = 10, memantine NNT = 3 - 8, and cognitive behaviour therapy NNT = 5 - 10. In contrast, the QALYs of patients were almost equal between IRR and usual care. In the cost-effectiveness analysis, the mean difference on EQ5D between the interventions was just small (0.04), with relatively small numbers of clinically relevant (≥ 0.5 sd) improved patients (not presented). This means that for psychiatric patients suffering from multiple psychogeriatric symptoms the EQ5D turned
out to be relatively irresponsible to change. This corresponds with the findings of Ballard and Katona, \cite{64-66}, who showed that clinically relevant improvement on BPSD had just small effects on regular quality of life measurements. \cite{64-66} Completing of EQ5D by proxy i.e. the caregiver may enhance the performance. All in all this means a drawback in comparing the effects of different interventions in a cost-utility study in psychogeriatrics. \cite{67} Further research is urgently needed on the discrepancy between the results on clinically relevant instruments and EQ5D. \cite{66,68-73} The same holds true for the higher costs of improved patients irrespective of type of intervention.

The strength of this study on economic evaluation of the RCT was that it was based on a relatively large sample size of patients. \cite{20} Furthermore, the benefit of full participation could be estimated as the relatively high percentage of dropouts did not differ significantly on the observed variables. The majority of dropouts could be ascribed to death of geriatric patients, being not significantly different in IRR and UC. The phenomenon of high dropout percentages is well known in geriatric research. \cite{2,5,14-19} Basically, it reflects the vulnerability of the psychogeriatric patients suffering from MPS. In addition, the relatively irresponsiveness of the patient's EQ5D compared to the significant beneficial change on the severity of MPS corresponds with results reported in literature. \cite{64,65,67,69,72,73}

Furthermore, this RCT was, according to our knowledge, one of the first comprehensive studies in a nursing home setting, with a relative large sample size that addressed integrative psychotherapeutic treatment of psychogeriatric patients and their caregivers.

What were the limitations of this study? First of all, RCT was not blinded. In a clinical study like this, blinding is not feasible. As the research co-workers had to visit the patients and caregivers personally, they knew the intervention history of the patients. Although we trained the research co-workers in proper administering the assessment instruments, it is not precluded that information bias emerged. Whether bias emerged in favour of IRR, is difficult to demonstrate. As the assessments at baseline showed just minor differences between IRR and usual care, excepted for somatic co-morbidity, the information bias at baseline seems to be limited. However, future studies have to be performed to strengthen the evidence, preferably as blinded RCTs. Another weakness was that only direct medical costs of patients were available; so other costs, specifically informal care at home were excluded. This may lead to an underestimation of costs at home, especially in usual care. In addition, in nursing home costs also food, social activities and the like are incorporated, resulting in an overestimation of nursing home costs, especially in IRR. Another relatively large limitation was the missing of cost-data of the caregiver. The more so, taking into account the significant beneficial effects of IRR on burden and competence of the caregiver which may have lowered their medical consumption. This means that the result of the economic evaluation was probably an underestimation of IRR. Furthermore, the study ended at 40 weeks. On the longrun, the trend in cost-effectiveness of IRR versus UC looked more favourable in IRR, specifically for caregivers.
Regarding generalization of the findings of this RCT, it is important to keep in mind that 50% of the eligible patients refused to participate. Relatively many of these patients lived with a spouse. The core motive for refraining participation was fear to be admitted in case of assignment to IRR. However, a post-hoc prognostic analysis showed that living together did not have prognostic quality, with respect to improvement on the primary outcome variable. In IRR the beneficial long term effects on multiple psychiatric symptoms of the patient and on the burden as well as the competence of caregiver are in line with those in literature of psychotherapeutic interventions on individual MPS. It is expected that by identifying the less effective therapeutic components and, consequently, by making them more effective or leaving them out, the beneficial effects of IRR will enlarge. To identify and, by consequence, to select the psychogeriatric patients and their caregivers with a relatively high likelihood to improve is another opportunity to enlarge the beneficial effects of IRR. To optimize medical decision making, the construction of a prognostic instrument identifying the vulnerable psychogeriatric patient along with his caregiver is clinically relevant.

5. Conclusion

On QALYs, no significant differences were found, while total medical costs of psychogeriatric patients in IRR were significantly higher. In contrast, fully participating patients and their caregivers improved in IRR significantly more on mean scores of the primary outcome variable severity of multiple psychiatric symptoms of the patient and of the secondary outcome variables general caregiver burden and competence of the caregiver, with ICERs varying from € 130.-- to € 540.--. The large discrepancy between QALYs and ICERs due to the relative irresponsive-ness of EQ5D to clinically relevant change, found in this study on psychogeriatric patients may mean a drawback in cost-utility studies in psychogeriatrics. It demands further research on validation of EQ5D in intervention studies with psychogeriatric patients. Considering all available evidence, the surplus costs of IRR are considered acceptable when the beneficial effects were taken into account on the high societal costs of suffering from multiple psychiatric symptoms of psychogeriatric patients and high burden of caregivers. To optimize the cost-utility and cost-effectiveness of IRR, the construction of a tool enabling to identify suitable psychogeriatric patients and caregivers for IRR is of high economical and clinical interest. Such a tool would contribute to optimize medical decision making based on an economical evaluation. Future studies have to be performed to strengthen the evidence, preferably as blinded RCTs.
References


32. Bakker TJEM, Duivenvoorden HJ, van der Lee J, Olde Rikkert M, Beekman ATF, Ribbe MW. Integrative psychotherapeutic nursing home programme to reduce multiple psychiatric symptoms of psychogeriatric patients and caregiver burden: a randomized controlled trial. 2010. (submitted)
40. Teunisse, S. Clinimetrics in Dementia, Dissertation, University of Amsterdam, 1997.
63. Bakker TJEM, Duivenvoorden HJ, van der Lee J, Olde Rikkert M, Beekman ATF, Ribbe MW. Benefit of integrative psychotherapeutic nursing home programme to reduce multiple psychiatric symptoms of psychogeriatric patients and caregiver burden after six months follow-up; a randomized controlled trial. (2010, in preparation)
Figure 1. Flow chart describing progress of patients through randomized controlled trial

Eligible patients (n = 336)

<table>
<thead>
<tr>
<th>Not randomized</th>
<th>n = 168</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refusal of referral/treatment</td>
<td>n = 152</td>
</tr>
<tr>
<td>Refusal of participation</td>
<td>n = 9</td>
</tr>
<tr>
<td>Reasons unknown</td>
<td>n = 7</td>
</tr>
</tbody>
</table>

Randomization  
(n = 168)

Intervention as allocated  (n=81)  Did not receive standard
Intervention as allocated  n = 1

Time 1:  
available:  n = 78  
death:  n = 2  
refusal:  n = 1  
loss:  n = 0  
total drop out:  n = 3  
4 %

Time 2:  
available:  n = 69  
death:  n = 10  
refusal:  n = 1  
loss:  n = 1  
total drop out:  n = 12  
15 %

Time 3:  
available:  n = 54  
death:  n = 24  
refusal:  n = 2  
loss:  n = 1  
total drop out:  n = 27  
33 %

Intervention as allocated  (n=87)  Did not receive experimental
Intervention as allocated  n = 1

Time 1:  
available:  n = 83 ¹)  
death:  n = 4  
refusal:  n = 0  
loss:  n = 0  
total drop out:  n = 4  
5 %

Time 2:  
available:  n = 77 ²)  
death:  n = 9  
refusal:  n = 0  
loss:  n = 1  
total drop out:  n = 10  
12 %

Time 3:  
available:  n = 64 ³)  
death:  n = 23  
refusal:  n = 0  
loss:  n = 0  
total drop out:  n = 23  
26 %

¹) Fisher’s Exact test for dropout * condition p 1.00 (two-tailed)  
²) Fisher’s Exact test for dropout * condition p 0.494 (two-tailed)  
³) Fisher’s Exact test for dropout * condition p 0.138 (two-tailed)
Table 1. General details of participants, distinguished by intervention

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>IRR n=81</th>
<th>UC n=87</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>gender (females)</td>
<td>66.7%</td>
<td>62.1%</td>
<td>0.63</td>
</tr>
<tr>
<td>age (in years), mean (sd)</td>
<td>79.8 (6.1)</td>
<td>81.5 (7.1)</td>
<td>0.10</td>
</tr>
<tr>
<td>marital status: alone</td>
<td>77.8%</td>
<td>80.5%</td>
<td>0.71</td>
</tr>
<tr>
<td>educational level: low</td>
<td>67.5%</td>
<td>68.7%</td>
<td>0.90</td>
</tr>
<tr>
<td>domicile: at home</td>
<td>76.5%</td>
<td>66.7%</td>
<td>0.17</td>
</tr>
<tr>
<td>primary caregiver: spouse</td>
<td>17.3%</td>
<td>13.8%</td>
<td>0.33</td>
</tr>
<tr>
<td>DSM-IV dementia, (axis-I), count (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dementia of the Alzheimer’s type</td>
<td>18.5%</td>
<td>17.2%</td>
<td>0.84</td>
</tr>
<tr>
<td>vascular dementia</td>
<td>23.5%</td>
<td>25.3%</td>
<td>0.86</td>
</tr>
<tr>
<td>dementia due to other conditions</td>
<td>16.0%</td>
<td>19.5%</td>
<td>0.69</td>
</tr>
<tr>
<td>amnestic/cognitive disorders</td>
<td>32.1%</td>
<td>31.0%</td>
<td>1.00</td>
</tr>
<tr>
<td>other</td>
<td>6.2%</td>
<td>2.3%</td>
<td>0.26</td>
</tr>
<tr>
<td>DSM-IV personality disorders (axis-II), count (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>16.0%</td>
<td>9.2%</td>
<td>0.24</td>
</tr>
<tr>
<td>GDS-deterioration, mean (sd)</td>
<td>4.2 (0.7)</td>
<td>4.3 (0.9)</td>
<td>0.62</td>
</tr>
<tr>
<td>somatic co-morbidity (ICD-10), mean (sd)</td>
<td>5.6 (2.6)</td>
<td>4.5 (2.4)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Caregiver characteristics</th>
<th>IRR n=81</th>
<th>UC n=87</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>gender (females)</td>
<td>70.5%</td>
<td>61.7%</td>
<td>0.32</td>
</tr>
<tr>
<td>age (in years), mean (sd)</td>
<td>58.6 (11.9)</td>
<td>58.9 (12.0)</td>
<td>0.86</td>
</tr>
<tr>
<td>marital status: living together</td>
<td>91.4%</td>
<td>94.8%</td>
<td>0.52</td>
</tr>
<tr>
<td>educational level: low</td>
<td>4.3%</td>
<td>2.6%</td>
<td>0.39</td>
</tr>
</tbody>
</table>

1) Fisher’s Exact Test (twotailed)
2) t-Test (twotailed)
3) Pearson Chi-square (twotailed)
<table>
<thead>
<tr>
<th></th>
<th>T1 (baseline measurement)</th>
<th>T3 (six months follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR</td>
<td>UC</td>
</tr>
<tr>
<td><strong>range</strong></td>
<td>high score</td>
<td>n</td>
</tr>
<tr>
<td><strong>Psychiatric function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>disorders patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(by caregiver)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPI-sum-severity</td>
<td>0 to 144</td>
<td>(-)</td>
</tr>
<tr>
<td>Caregiver burden</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregiver burden (CB)</td>
<td>0 to 100</td>
<td>(-)</td>
</tr>
<tr>
<td>Competence (CCL)</td>
<td>28 to 112</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Cognitive functioning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>0 to 30</td>
<td>(+)</td>
</tr>
<tr>
<td>Barthel Index (BI)</td>
<td>0 to 20</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Quality of life patient</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ5D</td>
<td>-0.59 to 1.00</td>
<td>(+)</td>
</tr>
</tbody>
</table>

* + = high score is beneficial, - = high score is unfavourable
Table 3. Mean costs (€) and QALY after 40 weeks, distinguished by Intervention; Multiple imputation (MI)

<table>
<thead>
<tr>
<th></th>
<th>IRR1</th>
<th>95% CI</th>
<th>UC2</th>
<th>95% CI</th>
<th>IRR-UC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>week 40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QALY</td>
<td>0.37</td>
<td>0.31 - 0.43</td>
<td>0.39</td>
<td>0.35 - 0.43</td>
<td>-0.02</td>
<td>-0.10 - 0.06</td>
</tr>
<tr>
<td>direct</td>
<td>42979.00</td>
<td>39650.92 - 46307.08</td>
<td>36299.00</td>
<td>33082.64 - 39515.76</td>
<td>4572.00</td>
<td>346.24 - 8797.76</td>
</tr>
</tbody>
</table>

1) Integrative Reactivation and Rehabilitation
2) Usual care

Table 4. Mean costs (€) after 40 weeks for the individual outcome variables, distinguished by Intervention; Complete case analysis (CC)

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>95% CI</th>
<th>mean</th>
<th>95% CI</th>
<th>mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>week 40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home care</td>
<td>21.05</td>
<td>-20.21 - 62.31</td>
<td>2895.01</td>
<td>921.53 - 4868.49</td>
<td>-2873.96</td>
<td>-4847.88 - 900.04</td>
</tr>
<tr>
<td>Day care</td>
<td>0.00</td>
<td>0.00 - 0.00</td>
<td>2773.18</td>
<td>433.60 - 4124.76</td>
<td>-2279.18</td>
<td>-4124.76 - 433.60</td>
</tr>
<tr>
<td>Hospital</td>
<td>964.74</td>
<td>27.66 - 1901.82</td>
<td>420.34</td>
<td>-49.61 - 890.29</td>
<td>544.40</td>
<td>-503.93 - 1592.73</td>
</tr>
<tr>
<td>Nursing home (incl. IRR)</td>
<td>27675.61</td>
<td>22724.36 - 32626.86</td>
<td>20123.51</td>
<td>14231.46 - 26015.56</td>
<td>7552.10</td>
<td>-144.08 - 15248.28</td>
</tr>
<tr>
<td>Service home</td>
<td>4902.63</td>
<td>2371.74 - 7433.52</td>
<td>4033.14</td>
<td>1624.22 - 6442.06</td>
<td>869.49</td>
<td>-2624.56 - 4363.54</td>
</tr>
<tr>
<td>Other care</td>
<td>149.16</td>
<td>64.68 - 233.64</td>
<td>757.05</td>
<td>138.89 - 1375.21</td>
<td>-607.89</td>
<td>-1231.80 - 16.02</td>
</tr>
</tbody>
</table>

1) Integrative Reactivation and Rehabilitation
2) Usual care

Table 5. Costeffectiveness after 40 weeks; distinguished by Intervention; ICER-approach

<table>
<thead>
<tr>
<th></th>
<th>Costs</th>
<th>Effects</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR</td>
<td>UC</td>
<td>IRR-UC</td>
</tr>
<tr>
<td>WEEK 40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPI-sum-severity (--)</td>
<td>33713.19</td>
<td>30508.23</td>
<td>21.78</td>
</tr>
<tr>
<td>Caregiver burden (CB)</td>
<td>33713.19</td>
<td>30508.23</td>
<td>24.76</td>
</tr>
<tr>
<td>Caregiver competence (CCL)</td>
<td>33713.19</td>
<td>30508.23</td>
<td>10.35</td>
</tr>
<tr>
<td>MMSE</td>
<td>33713.19</td>
<td>30508.23</td>
<td>-1.25</td>
</tr>
<tr>
<td>Barthel-Index (BI)</td>
<td>33713.19</td>
<td>30508.23</td>
<td>-3.61</td>
</tr>
<tr>
<td>EQ5D patient</td>
<td>33713.19</td>
<td>30508.23</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*) + = high score is beneficial, - = high score is unfavourable