Economic evaluation in mental healthcare

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Chapter 2

Cost-effectiveness of the HIT programme in patients with schizophrenia and persistent auditory hallucinations

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Abstract

Objective: To examine the cost-effectiveness of Hallucination focused Integrative Treatment (HIT) in patients with schizophrenia and a history of persistent auditory hallucinations.
Method: Costs, in and outside the healthcare sector, and outcomes were registered prospectively during a period of 18 months for patients who received the HIT programme and for patients in the care as usual condition. The Positive And Negative Syndrome Scale (PANSS) was used as main outcome measure in the cost-effectiveness analysis. Bootstrap analyses provided additional information on the skewly distributed costs.
Results: Mean costs per patient in the HIT group ($18,237) were lower than the mean costs per patient in the care as usual group ($21,436). Results of the PANSS were slightly in favour of the HIT group.
Conclusion: There appears to be no significant cost-effectiveness advantage of the HIT programme over care as usual. Additional analyses indicated that future application of the HIT programme will, in most cases, lead to a reduction of (non)medical costs.

Introduction

Schizophrenia is a serious and complex mental disorder with a large impact on the lives of patients and their social environment. As schizophrenia is a chronic condition and patients make intensive use of mental healthcare resources (1), the consequences for national healthcare expenses are substantial as well (2). In recent years, policy-makers have been stimulating the development of interventions and healthcare services that could lead to an improvement in the relation between costs and health outcomes associated with schizophrenia (3-5).

Schizophrenia-related research initially concentrated on the effectiveness of unimodular therapies, in particular medication treatment, but results were generally disappointing (6). It is only for the last decade that the effect of adjunctive treatment, e.g. family treatment (7) and cognitive behaviour therapy (8), has been studied. Adjunctive treatments proved to be more effective as to signs, relapse and rehospitalisation (9). Despite these improvements, the majority of patients with schizophrenia continue to have disabling residual symptoms and remain handicapped in social functioning. Gradually, consensus has been growing that optimal treatment of schizophrenia requires integrative treatment programmes (10), although the exact composition of such programmes remains open for debate.

In 1994, Hallucination focused Integrative Treatment (HIT) was developed at the University Hospital Groningen. The HIT programme aims at integration of cognitive behaviour therapy with neuroleptics, coping training, psycho-education, motivational interventions, rehabilitation, and single family treatment. In naturalistic studies the HIT programme appeared quite effective in reducing signs and symptoms in chronic therapy-refractory patients (11) as well as in first episode psychotic adolescents (12). Positive results of the HIT programme remained over time (13).

In contrast to the number of studies on effectiveness, studies on the cost-effectiveness of interventions for schizophrenia are still rare, although information on cost-effectiveness is highly relevant for policy decisions in healthcare. Only a few studies have examined costs and outcomes of some of the elements of the integrative HIT programme. One study situated in the UK (14) focused not only on the effectiveness of cognitive behaviour therapy for patients with psychosis (most patients had a diagnosis of schizophrenia), but also on the cost-effectiveness of this therapy. Results indicated that positive health outcomes were retained over a period of 18 months. Unfortunately, the economic analyses were based on incomplete information on costs of only a small number of subjects. The authors concluded that cognitive behaviour therapy could be a cost-effective intervention for this subject group. In another study (15), economic consequences of behavioural family

treatment in schizophrenia were estimated. This treatment proved to be effective, relapse rates decreased significantly, and additional costs of the intervention were compensated by decreased costs of mental health services used. Finally, the majority of currently available studies focused on the cost-effectiveness of antipsychotic medication, including the (more expensive) atypical antipsychotics, but the scope of the conducted economic evaluations in this field is narrow; cost analyses are usually restricted to direct medical costs (16-18). In sum, information on the cost-effectiveness of interventions for schizophrenia is scarce and inconclusive. One of the main shortcomings of the available economic evaluations is the limited number of included cost categories. Most studies concentrate on (often incomplete) direct medical costs without considering the inclusion of direct and indirect non-medical costs (19), like costs of informal care and productivity losses. In particular, these latter costs can be substantial in patients with schizophrenia (20, 21). However, the amount of costs depends, to some extent, on the methods used (22) to quantify these losses.
The purpose of the current paper was to describe the cost-effectiveness analysis of the HIT programme. For the assessment of the cost-effectiveness of the HIT programme, costs, inside and outside the healthcare sector, and health outcomes were compared between patients who received the HIT programme and patients who received care as usual.

Material and methods

Study design
The conducted cost-effectiveness analysis was an integral part of a study on the effectiveness of the HIT programme. Detailed information on the HIT programme, the design and results of the clinical study is described elsewhere (12, 13, 23). The study was designed as a randomised controlled clinical trial. Recruitment of patients took place in the northern and eastern part of the Netherlands. Patients were included if they met the following criteria: suffering from auditory hallucinations despite adequate treatment for at least two years, diagnosis (DSM-IV) within the schizophrenia spectrum, treated with at least two antipsychotic drugs during an adequate period of time, no previous treatment for auditory hallucinations with cognitive behaviour therapy, no current abuse of psychoactive drugs or alcohol and an IQ above 80. A battery of instruments was constructed to measure, among other things, symptoms and burden [Auditory Hallucination Rating Scale (AHRS); 24], psychopathology [Positive And Negative Syndrome

Scale (PANSS); 25] and social disabilities [Groningen Social Disabilities Scale (GSDS); 26]. Power analyses indicated that a sample size of 26 patients in each group would achieve 80% power to detect a 20% difference in PANSS score at the 5% significance level (mean condition 1: 30.3, mean condition 2: 37.7; sd 9.5). Randomisation was carried out by the Office for Medical Technology Assessment of the University Hospital Groningen. Patients were randomly assigned to the interventions, HIT or care as usual (CAU). CAU for patients with chronic schizophrenia in the Netherlands consists of medication monitoring, psycho-education and supportive counselling. Measurement was carried out by independent researchers and took place at the time of inclusion (T0), after 9 months (T9, the end of the treatment phase), and after 18 months (T18, the end of the follow-up period).

Patients

Between 1998 and 2000, in total 76 patients were randomised (37 in the HIT group and 39 in the CAU group). Ten patients withdrew from the study before T18 and one patient died of natural courses. For two other patients, information on costs during the treatment phase or follow-up period was missing and they were excluded from the economic analyses. Therefore, results of the cost-effectiveness analyses are based on the information of the remaining 63 patients (83% of the originally included patients), 31 in the HIT group and 32 in the CAU group. Relevant characteristics of the 13 patients who were excluded did not differ significantly from the other patients at the time of inclusion.

Design of the cost-effectiveness analysis

Cost-effectiveness analysis is a form of full economic evaluation, in which costs and consequences of a health programme or treatment and at least one alternative are calculated and presented in a ratio of incremental costs to incremental effects (19, 27). In the present study, costs and outcomes of patients who received the HIT programme were compared with those of patients in the CAU group. Main outcome measure of the cost-effectiveness analysis was the aggregated score on the PANSS (25). The PANSS is a 30-item, semi-structured interview with the patient on psychiatric symptoms (including hallucinations). Lower scores on the PANSS reflect better functioning. The costs per point improvement on the PANSS were expressed by means of the incremental cost-effectiveness ratio (ICER):

$$\text{ICER} = \frac{(C_{HIT} - C_{CAU})}{(P_{HIT} - P_{CAU})}$$

where C_{HIT} = mean costs per patient in the HIT group, C_{CAU} = mean costs per patient in the CAU group, P_{HIT} = mean PANSS difference score in the HIT group, P_{CAU} = mean PANSS difference score in the CAU group.

The cost-effectiveness analysis was conducted on an intention-to-treat basis, i.e. all relevant costs and effects of patients were assigned to the intervention to which they were randomised. Costs and outcomes were registered prospectively during a period of 18 months.

Assessment of costs and unit prices

The cost analyses included all cost types that were expected to differ between groups. As the study was performed from a societal perspective, the analyses did not only focus on direct medical costs, but also assessed direct and indirect non-medical costs. Table 1 shows the various cost categories and types of costs that were included in the analyses.

Table 1. Included cost categories and types of costs

Direct medical costs	Direct non-medical costs	Indirect non-medical costs
Cognitive therapy	Travel costs	Productivity losses paid labour
Inpatient care	Invested time	
Sheltered accommodation/day care	Informal care	
Outpatient and community care	Out-of-pocket costs	
General healthcare services		
Day activity institutions		
Medication		

Costs of cognitive therapy, travelling and invested time only applied to the treatment phase of the HIT programme. Costs of travelling and invested time were expenditures of patients who attended cognitive therapy sessions of the HIT programme, which was provided at a few locations in the study area. In the current study, informal care consisted mainly of invested time by relatives and acquaintances in assisting the patient. Additional costs related to the illness, like costs of damage caused by the patient, are entitled as out-of-pocket costs. The friction cost method (28, 29) was used to estimate the costs of productivity losses caused by illness-related absences from work. Under this method, production losses are assumed to be confined to the period needed to replace the sick worker: the friction period. In this study, the values used for lost productivity are estimated by the duration of absence and the net income of the patient during this period. Quantities of used resources were registered prospectively, i.e. within the context

of the current study, for all patients included in the analyses. The information was primarily collected by means of a questionnaire developed for the purpose of the current study. This questionnaire focused on various types of costs during T0-T9 and T9-T18 and assessed, among others, the number of admissions to psychiatric hospitals, the number of days patients stayed in sheltered accommodations, the number of visits to a psychiatrist or psychologist, and the number of sick leave days of patients with paid labour. Additional information, for instance medication use and the number of cognitive therapy sessions in the HIT group, was registered by various healthcare professionals involved.
Unit prices, the price of one unit of each included cost type (available on request), were mainly based on Dutch standard prices (30) in order to facilitate comparability with previous and future cost-effectiveness studies. However, for various cost types standard prices were not available and true costs of used resources were estimated. Finally, for the unit price of crisis interventions the available tariff for regular crisis intervention during the daytime was applied. All unit prices are based on the price level of the Dutch guilder in the year 2000. Results will be presented in US dollars (1 dollar = 2.19 guilder; rate of exchange at January 2000).

Discounting and sensitivity analyses
Costs and outcomes that occur after 1 year are usually discounted in cost-effectiveness analyses, because people are assumed to prefer immediate over postponed consumption (27). Most of the costs during the follow-up period (9 months after inclusion up until 18 months after inclusion) occurred in the second year. For the sake of simplicity, it was assumed that all costs during the follow-up period took place in the second year and were, therefore, eligible for discounting. The same assumptions were also applied to the health outcomes during the follow-up period. Following the recommendations of the Dutch guidelines for studies on costs (30), a discount rate of 4% was used for costs and health outcomes. Both univariate and multivariate sensitivity analyses were planned in order to provide information on the robustness of the results of the economic analyses. Only cost variables that contributed considerably to the total amount of costs (at least 10%) were included in these analyses. Additional sensitivity analyses focused on the influence of varying discount rates. Finally, the bootstrap method (31) was used to nonparametrically estimate the 95% confidence interval of calculated costs. By using this method, a large number of simulated patient populations (in this study 1000) can be created by randomly selecting patients (with replacement) from the original patient population.

Statistical analyses

All analyses were carried out using SPSS for Windows (version 10.0.7). Cost differences between groups were mainly analysed using the Mann-Whitney U test for independent samples since the vast majority of cost variables was skewly distributed. Normally distributed variables were tested with Student's t-test for independent samples. All significance test results involved two-tailed probabilities with alpha set at 0.05. Cost differences were presented descriptively when the number of patients utilising a certain cost type was (in at least one of the groups) smaller than three (32).

Results

Patients

Details of patients included in the economic analyses are briefly described in Table 2. At the time of inclusion, the mean age of patients in the HIT and CAU group was 36 and 35 years, respectively.

Table 2. Characteristics of patients included in the economic analyses

	HIT group (n=31)	CAU group (n=32)	Significance
Age			
Mean age in years (sd)	36.3 (11.1)	35.3 (10.6)	n.s. [1]
Gender			
Male	55%	53%	n.s. [2]
Diagnoses			
Paranoid schizophrenia	77%	81%	
Schizo-affective disorder	13%	16%	n.s. [2]
Psychosis NOS	10%	3%	
Hallucinations			
Duration (years) of hallucinations (sd)	13.2 (11.5)	10.3 (7.7)	n.s. [1]

[1] Student's t-test, [2] Chi-square

The number of males and females did hardly differ between groups. Most patients had diagnoses of paranoid schizophrenia. The mean duration of hallucinations was 13 years for patients in the HIT group, and 10 years for patients in the CAU group. There were no significant differences between treatment groups on any of these characteristics, nor were there any differences between groups in healthcare service use during a period of 9 months prior to the study.

Costs during the study period

Information on direct medical costs and service utilisation during the study period is presented in Table 3.

Table 3. Direct medical costs during study period (T0-T18)

Healthcare services and cost types	Costs ($) of HIT group (n=31)				Costs ($) of CAU group (n=32)				Sign. of difference[2]
	mean	sd	median	n'[1]	mean	sd	median	n'[1]	
HIT programme									
Cognitive therapy	1059	536	1054	31	-	-	-	-	-
Training[3]	177	-	-	31	-	-	-	-	-
Supervision[3]	381	-	-	31	-	-	-	-	-
(Semi-)inpatient care									
Psychiatric hospital admission	23550	18417	22117	4	5817	12859	623	6	n.s.
Sheltered accommodation	33096	11618	34415	9	35232	8763	39054	13	n.s.
Day care	1776	179	1776	2	2284	1436	2284	2	-[4]
Outpatient/community care									
Psychiatrist	207	212	114	20	281	345	143	29	p<.02
Psychologist	531	231	531	5	352	321	314	5	n.s.
Social-psychiatric nurse	267	261	226	13	476	269	415	16	n.s.
Social worker	72	51	50	5	88	103	88	2	-[4]
Crisis intervention	130	0	130	2	187	88	187	2	-[4]
Psychiatric home care	440	508	221	6	2329	3274	723	12	n.s.
Other outpatient care	227	-	227	1	892	838	790	4	-[4]
CAD [5]	-	-	-	0	-	-	-	0	-[4]
General healthcare									
General practitioner	138	188	74	9	64	80	34	13	n.s.
Alternative healthcare	94	66	84	3	45	26	49	3	n.s.
Emergency care	-	-	-	0	-	-	-	0	-[4]
Other general healthcare	-	-	-	0	379	-	379	1	-[4]
Day activity institutions									
Day activity centre	1700	1574	1756	7	1400	1545	1322	15	n.s.
Drop-in centre	1492	2509	61	3	964	1300	232	11	p<.02
Other day activity institutions	858	770	1055	3	712	963	317	5	n.s.
Medication									
Prescribed medication	1807	1500	1585	31	2255	1750	1810	32	n.s.
Non-prescribed medication	62	-	62	1	139	154	139	2	-[4]

[1] n' represents the number of patients using the health services and cost types concerned. Mean and median values are based on these patients.
[2] All patients of both groups were included in these analyses as long as there was no missing patient data on the variable involved.
[3] Constant value, calculated for the current number of included patients.
[4] Not tested due to small number of patients using this service.
[5] CAD = Consultation Office for Alcohol and Drug Addiction.

The HIT programme was provided during the first 9 months of the study and the associated costs (i.e. costs of therapy, training and supervision presented in Table 3, but also travel and time costs of patients presented in Table 4) did not apply to patients in the CAU group. Total costs of the HIT programme were $52,646 (mean costs per patient were $1,698) and constituted 9% of the total costs of patients in the HIT group. Significant differences in favour of patients in the HIT group were found for a few cost types; costs associated with consulting psychiatrists, and costs of visiting drop-in centres (non-intensive social support).
Table 4 displays the direct and indirect non-medical costs of both groups during the study period. No significant differences between groups were found for these cost types. Mean total costs per patient (sum of all costs in Table 3 en 4) in the HIT group during the entire study period were $18,237 (median costs $6,840). For patients in the CAU group, mean total costs per patient were $21,436 (median costs $12,677). Note that the total costs were substantially influenced by the costs of sheltered accommodations and admissions to psychiatric hospitals. Differences between the total costs of both treatments were not statistically significant.

Table 4. Direct en indirect non-medical costs (T0-T18)

Services and cost types	Costs ($) of HIT group (n=31)				Costs ($) of CAU group (n=32)				Sign. of diffe-rence[2]
	mean	sd	median	n'[1]	mean	sd	median	n'[1]	
Travel costs	135	171	84	14	-	-	-	-	-
Time costs	137	66	130	5	-	-	-	-	-
Informal care	1420	1167	1245	11	1876	1300	1739	14	n.s.
Out-of-pocket costs	351	434	351	2	-	-	-	0	-[3]
Productivity losses	2095	1234	1973	5	1834	1129	1834	2	-[3]

[1] n' represents the number of patients using the services and cost types concerned. Mean and median values are based on these patients.
[2] All patients of both groups were included in these analyses as long as there was no missing patient data on the variable involved. Costs were $0,- for patients who did not use the service concerned.
[3] Not tested due to small number of patients using this cost type.

PANSS results

Results of the PANSS, the main outcome measure in the cost-effectiveness analysis, are listed in Table 5. Note that lower scores on the PANSS reflect better functioning. Results of T0 and T18 were relevant for the calculation of the incremental cost-effectiveness ratio (ICER). Difference scores were computed by subtracting the discounted T18 score from the results of T0. Although these difference scores were in favour of the HIT group, differences did not approach a statistically significant level.

Table 5. PANSS results [1]

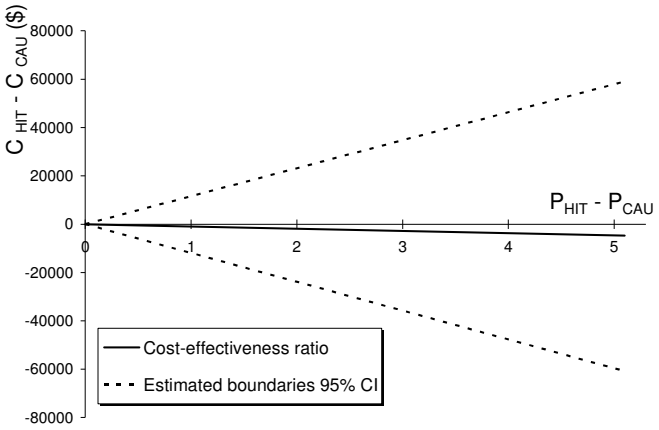
PANSS scores	HIT group (n=31)	CAU group (n=32)	Significance of difference
PANSS T0	57.1	60.2	n.s.
PANSS T9	51.0	61.7	p<.01
PANSS T18	51.1	57.3	n.s.

[1] = Listed PANSS scores are mean values.

Cost-effectiveness analysis

There were no significant differences between groups in changes in PANSS scores by T18, nor in total costs over the study period. Thus, there is no clear cost-effectiveness advantage of one condition over another. However, the trend toward lower mean costs and an improvement in PANSS scores for the HIT group suggested that calculation of an ICER would be informative. In order to enable generalisation of the current results to future situations, it was decided to assess the ICER in combination with the accompanying 95% confidence interval. For the cost component of the cost-effectiveness analysis, mean costs per patient during the study period were used. As an improvement in functioning is reflected by a decrease in the PANSS score, it was decided to multiply the calculated PANSS difference scores by –1. In this way, improved functioning is expressed in a positive difference score, which simplifies the interpretation of the ICER.

Figure 1. Cost-effectiveness ratio and estimated 95% confidence interval



The calculated value of the ICER, using the formula described in the method section, was – 936. This negative value indicates that patients in the HIT group generated fewer costs and had better results on the PANSS. The estimated 95% confidence interval is graphically presented along with the calculated ICER in Figure 1. As negative ICERs may cause some inaccuracies with regard to the estimation of confidence intervals (33), the presented boundaries should be considered as approximations.

Sensitivity analyses

For the uni- and multivariate sensitivity analyses, cost variables that covered at least 10% of total costs per patient group were identified. In the univariate analyses, identified cost types per group were increased and decreased one at a time by 20% and differences in total costs were subsequently tested. However, no significant differences were found. In the multivariate analyses, all identified cost types of one group were increased while the identified cost types of the other group were decreased by 20%. Significant differences ($p<.03$) were found when identified costs of the HIT group were decreased and identified costs of the CAU group were increased. Variations of the discount rate (3% and 5% instead of 4%) only had minor consequences for the results of the analyses.

In order to provide additional information for the interpretation of the results of the economic analyses, the bootstrap method was used to determine the range of future differences in costs (incremental costs) associated with the HIT programme and CAU. The median cost difference between both interventions calculated with the bootstrap method was - $3,413. The lower and upper boundaries of the accompanying 95% confidence interval were - $12,050 and + $6,637, respectively. Again, negative values indicate fewer generated costs for patients in the HIT group.

Discussion

This paper presented the cost-effectiveness analysis of the HIT programme, an integrated treatment for persistent auditory hallucinations in patients with schizophrenia. In the cost-effectiveness analysis, a comparison was made between costs and outcomes of patients who received either the HIT programme or CAU.
The assessment of healthcare utilisation and associated costs was an essential part of the economic analyses. Results indicated that the total amount of generated costs of both patient groups was influenced substantially by the costs of sheltered accommodations and admissions to psychiatric hospitals. These results are in accordance with previous studies on service utilisation and costs of patients with chronic schizophrenia (1, 34, 35). Costs of medication (about 10% of total costs) were somewhat higher in the present study compared with other studies (2). It is most likely that these higher medication costs were at least partly due to increasing use of expensive atypical antipsychotics in recent years. Furthermore, results of the cost analyses indicated that the mean costs of the HIT programme per patient were $1,698 during a treatment phase of nine months. These costs constituted 9% of the total costs of patients in the HIT group.
As the cost-effectiveness analysis was performed from a societal perspective, costs outside the healthcare sector were also included in the analyses. The total amount of non-medical costs was highly influenced by costs related to informal care (71% of total non-medical costs). In the present study, costs associated with productivity losses only had a minor influence on the total amount of non-medical costs. This finding is in contrast with some other studies (20, 21) where productivity costs constituted a substantial part of total costs, which is mainly due to the methods used to quantify productivity losses (22).
The absence of statistically significant differences in total costs seems to be the result of the skewed distribution of cost variables in combination with the size of the study population. This problem is quite common in economic analyses (14, 36). Fortunately, there are several methods that can (partially) deal with the uncertainties surrounding skewly distributed costs. In the present study the bootstrap method was used (31). This method provided additional information on the skewly distributed costs by nonparametrically determining the 95% confidence interval. Results indicated that future cost differences will, in most cases, be in favour of the HIT programme.
Cost-effectiveness analyses require the selection of a primary outcome measure. In the present study the PANSS was chosen for this purpose and power analyses were based on this instrument. Although differences between groups in total PANSS score were statistically significant at T9 and in favour of the HIT group, patients in

the CAU group improved considerably during the follow-up period, which led to a smaller and non-significant difference (still in favour of the HIT group) at T18. As a consequence, calculated difference scores for the entire study period (T18-T0) were in favour of the HIT programme, but did not demonstrate statistically significant differences between groups.
Additional evidence for the superiority of the HIT programme was found through the administered questionnaires on symptoms (AHRS), quality of life (WHOQoL-BREF: 37) and social functioning (GSDS). Results indicated that patients in the HIT group had more control over voices, experienced less subjective distress, and demonstrated less social disabilities than patients in the CAU condition (personal communication).
In conclusion, a simple comparison of costs and outcomes indicates that there is no significant cost-effectiveness advantage of the HIT programme over CAU. Additional analyses demonstrated that future application of the HIT programme will, in most cases, lead to a reduction of societal costs associated with chronic schizophrenia. At the present time, only a small number of studies has focused on the cost-effectiveness of interventions for patients with schizophrenia. As societal costs of schizophrenia are high and policy decisions in healthcare are increasingly based on information concerning costs and outcomes, it is to be expected that the number of cost-effectiveness analyses in this field of expertise will expand considerably in the following years, which may add to the interpretation of the results of the present study as well.

References

1. Wiersma D, Sytema S, Van Busschbach J, Schreurs M, Kroon H, Driessen G. Prevalence of long-term mental health care utilization in the Netherlands. Acta Psychiatr Scand 1997; 96: 247-253.

2. Knapp M. Schizophrenia costs and treatment cost-effectiveness. Acta Psychiatr Scand 2000; 102 (Suppl. 407): 15-18.

3. Hallam A, Knapp M, Beecham J, et al. Eight years of psychiatric reprovision: An Economic evaluation. In: Knapp M, eds. The Economic Evaluation of Mental Health Care. Aldershot: Arena, 1995: 103-124.

4. Kavanagh SM, Steenbekkers JHM. Costs of extramuralisation in mental health care. TNO Prevention and Health, report PG/VGZ/2000.010. Leiden: TNO, 2000.

5. Pijl YJ, Kluiter H, Wiersma D. Change in Dutch mental health care: an evaluation. Soc Psychiatry Psychiatr Epidemiol 2000; 35: 402-407.

6. Young JL, Zonana HV, Shepler L. Medication noncompliance in schizophrenia: codification and update. Bull Am Acad Psychiatry Law 1986; 14: 105-122.

7. McFarlane WR, Lukens E, Link B et al. Multiple-family groups and psychoeducation in the treatment of schizophrenia. Arch Gen Psychiatry 1995; 52: 679-687.

8. Drury V, Birchwood M, Cochrane R, Macmillan F. Cognitive therapy and recovery from acute psychosis: a controlled trial. I. Impact on psychotic symptoms. Br J Psychiatry 1996; 169: 593-601.

9. Mojtabai R, Nicholson RA, Carpenter BN. Role of psychosocial treatments in management of schizophrenia: a meta-analytic review of controlled outcome studies. Schizophr Bull 1998; 24: 569-587.

10. Brenner HD, Hirsbrunner A, Heimberg A. Integrated psychological therapy programme: training in cognitive and social skills for schizophrenic patients. In: Corrigan PW, Yudovsky SC, eds. Cognitive rehabilitation for neuropsychiatric disorders. Washington: APP, 1996.

11. Jenner JA, Van de Willige G, Wiersma D. Effectiveness of cognitive therapy with coping training for persistent auditory hallucinations: a retrospective study of attenders of a psychiatric out-patient department. Acta Psychiatr Scand 1998; 98: 384-389.

12. Jenner JA, Van de Willige G. HIT, hallucination focused integrative treatment as early intervention in psychotic adolescents with auditory hallucinations: a pilot study. Acta Psychiatr Scand 2001; 103: 148-152.

13. Wiersma D, Jenner JA, Van de Willige G, Spakman M, Nienhuis FJ. Cognitive behaviour therapy with coping training for persistent auditory hallucinations in schizophrenia: a naturalistic follow-up study of the durability of effects. Acta Psychiatr Scand 2001; 103: 393-399.

14. Kuipers E, Fowler D, Garety P et al. London-east Anglia randomised controlled trial of cognitive-behavioural therapy for psychosis. III: Follow-up and economic evaluation at 18 months. Br J Psychiatry 1998; 173: 61-68.

15. Tarrier N, Lowson K, Barrowclough C. Some aspects of family interventions in schizophrenia. II: Financial considerations. Br J Psychiatry 1991; 159: 481-484.

16. McCombs JS, Nichol MB, Johnstone BM, Stimmel GL, Shi J, Smith R. Antipsychotic drug use patterns and the cost of treating schizophrenia. Psychiatr Serv 2000; 51: 525-527.

17. Lewis M, McCrone P, Frangou S. Service use and costs of treating schizophrenia with atypical antipsychotics. J Clin Psychiatry 2001; 62: 749-756.

18. Revicki DA. Cost effectiveness of the newer atypical antipsychotics: a review of the pharmacoeconomic research evidence. Curr Opin Investig Drugs 2001; 2: 110-117.

19. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in Health and Medicine. Oxford: Oxford University Press, 1996.

20. Genduso LA, Haley JC. Cost of illness studies for schizophrenia: components, benefits, results, and implications. Am J Manag Care 1997; 3: 873-877.

21. Tarricone R, Gerzeli S, Montanelli R, Frattura L, Percudani M, Racagni G. Direct and indirect costs of schizophrenia in community psychiatric services in Italy. The GISIES study. Health Policy 2000; 51: 1-18.

22. Marcotte DE, Wilcox-Gök V. Estimating the employment and earning costs of mental illness: recent developments in the United States. Soc Sci Med 2001; 53: 21-27.

23. Jenner JA. HIT, an integrative treatment for patients with persistent auditory hallucinations. Psychiatr Serv 2002; 53: 897-898.

24. Haddock G. Auditory hallucination rating scale. Manchester: University of Manchester, 1994.

25. Kay SR, Opler LA, Lindenmayer JP. The Positive And Negative Syndrome Scale (PANSS): rationale and standardisation. Br J Psychiatry Suppl 1989; 7: 59-67.

26. Wiersma D, De Jong A, Kraaijkamp HJM, Ormel J. GSDS-II: the Groningen Social Disabilities Schedule, second version. Groningen: Rijksuniversiteit Groningen, 1990.

27. Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Oxford: Oxford University Press, 1987.

28. Koopmanschap MA, Rutten FFH, Van Ineveld BM, Van Roijen L. The friction cost method for measuring indirect costs of disease. J Health Econ 1995; 14: 171-189.

29. Koopmanschap MA, Van Ineveld BM. Towards a new approach for estimating indirect costs of disease. Soc Sci Med 1992; 34: 1005-1010.

30. Oostenbrink JB, Koopmanschap MA, Rutten FFH. Manual for cost studies, methods and standard prices for economic evaluation in health care [In Dutch: Handleiding voor kostenonderzoek, methoden en richtlijnprijzen voor economische evaluaties in de gezondheidszorg]. Amstelveen: Health Care Insurance Council, 2000.

31. Efron B, Tibshirani RJ. An introduction to the bootstrap. New York: Chapman & Hall, 1993.

32. Siegel S, Castellan NJ. Nonparametric statistics for the behavioral sciences. New York: McGraw-Hill, 1988.

33. Briggs AH, O'Brien BJ, Blackhouse G. Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies. Annu Rev Public Health 2002; 23: 377-401.

34. Marshall M, Crowther R, Almaraz-Serrano A et al. Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) acute day hospital versus admission; (2) vocational rehabilitation; (3) day hospital versus outpatient care. Health Technol Assess 2001; 5: 1-75.

35. Knapp M, Chisholm D, Leese M et al. Comparing patterns and costs of schizophrenia care in five European countries: the EPSILON study. Acta Psychiatr Scand 2002; 105: 42-54.

36. Gray AM, Marshall M, Lockwood A, Morris J. Problems in conducting economic evaluations alongside clinical trials. Lessons from a study of case management for people with mental disorders. Br J Psychiatry 1997; 170: 47-52.

37. WHOQoL group. Development of the World Health Organization WHOQoL-BREF Quality of Life Scale. Psychol Med 1998; 28: 551-558.