Economic evaluation in mental healthcare

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Chapter 7

Discussion
The economic evaluations presented in this thesis focused on interventions for persons who were diagnosed with major depressive disorder or schizophrenia. These disorders are considered to be among the most disabling (mental) illnesses, and are both associated with intensive healthcare utilisation and considerable costs for society. At the time when the presented studies were initiated, detailed information on economic aspects of interventions in mental healthcare was virtually absent for the Netherlands, and economic studies in the described patient populations were strongly needed to support policy decisions. The primary aim of the conducted studies was therefore to assess the cost-effectiveness of the interventions concerned and report results to decision-makers.

In the following section, the overall findings and interpretation of the economic evaluations that are part of this thesis will be discussed. The policy decisions that were based on these results will also be provided. Various methodological issues encountered in these evaluations will be presented in the context of the current literature. Based on the discussed methodological issues, recommendations will be made for the general design of future economic evaluations in the field of mental healthcare. Finally, recent (inter)national developments and economic benefits related to various other interventions studied in mental healthcare will be discussed, together with the relevance of improving the actual implementation of cost-effective interventions.

**Overall findings and the interpretation of results**

Chapters 2 through 5 presented the results of four cost-effectiveness studies in patients with major depressive disorder or schizophrenia. In these studies, a wide variety of interventions was compared with care as usual (CAU) in the patient populations concerned. Two interventions were aimed at depression: Cognitive Self-Therapy (*Chapter 3*) and a depression recurrence prevention programme (PEP: *Chapter 4*). The other two studies addressed interventions in patients with schizophrenia: Hallucination focused Integrative Treatment (HIT: *Chapter 2*) and guided discontinuation strategy (*Chapter 5*).

For two interventions (HIT and Cognitive Self-Therapy), costs and health outcomes were in favour of the interventions under study, although differences with CAU in terms of primary health outcomes were generally modest. Results of the study comparing three variants of PEP with CAU showed that basic PEP was associated with higher costs and worse health outcomes than CAU. Two enhanced versions of PEP (with psychiatric consultation and cognitive behavioural therapy)
also led to higher costs, but results of the primary health outcome were slightly better than in CAU. In the study on discontinuation strategy, no relevant differences could be found for costs or health outcomes when comparing results with CAU.

Besides simple comparisons of costs and health outcomes, various additional economic analyses were performed in the presented studies. These analyses included the calculation of incremental cost-effectiveness ratios as well as bootstrap analyses to provide information on the uncertainty surrounding the economic results. Furthermore, cost-effectiveness acceptability curves were assessed in most studies, which provided information on the probability of the interventions being cost-effective. This probability is based on what a decision-maker (or society) is willing to pay for an additional unit of health outcome (1).

Interpretation of the overall results of the various conducted economic analyses depends on whether one adopts a Bayesian decision-making framework, or applies a classical frequentist (statistical hypotheses testing) approach for inference (2). When using a frequentist approach, none of the interventions examined in this thesis can be considered cost-effective, i.e. there were no statistically significant differences for combined cost and health outcomes in any of the four studies. In fact, only few published economic evaluations would fulfil such frequentist criteria. Various authors have strongly argued for a Bayesian approach in recent years, which allows for probability statements that seem more relevant and appropriate in the context of decision-making (3). When interpreting the current results from a Bayesian perspective, HIT appears to be a cost-effective intervention for patients with persistent auditory hallucinations in comparison with CAU. Furthermore, the results of the economic analyses in the Cognitive Self-Therapy study are in support of implementing this intervention in the Dutch healthcare system. Interpretation of the economic results of the study on PEP is not favourable for the basic PEP intervention. Finally, the economic evaluation of guided discontinuation strategy provides no clear economic support for implementing such an approach, although there appear to be clinical advantages related to guided discontinuation for some of the studied patients.

The primary aim of the studies presented in Chapters 2 to 5 was to inform decision-makers on the cost-effectiveness of the interventions under study. The results of these four studies have been reported to the Dutch Ministry of Health, Welfare and Sport. Two of the examined interventions (HIT and Cognitive Self-Therapy) were eventually recommended for reimbursement within the Dutch healthcare system.
Methodological issues related to economic evaluation in (mental) healthcare

In this section, various methodological issues encountered in the presented studies will be discussed. Some are more specific for economic studies in the field of mental healthcare, whereas others have a broader scope.

Outcome measures: QALYs versus (disease-)specific health outcomes
Guidelines on the design of economic evaluations uniformly recommend the use of preference-based health outcomes, in particular Quality-Adjusted Life Years (QALYs: 4). An important advantage of such outcomes is the possibility of directly comparing findings across studies and illnesses. As described in Chapter 6, only few published economic evaluations in mental healthcare actually included QALYs (5, 6), due to various methodological concerns about this outcome measure (7). QALYs were assessed in three of the four economic evaluations presented in this thesis. In the study on guided discontinuation strategy (Chapter 5), QALYs formed the primary outcome measure. No differences were found between QALY results of the two study groups, which was in line with the results of various (secondary) clinical outcome measures. For the other two studies (HIT in Chapter 2, PEP in Chapter 4), QALYs were assessed in addition to the primary health outcomes on which power analyses were based. In the PEP study, QALYs could only be assessed for some of the included patients, results generally seemed to be in accordance with other outcome measures favouring CAU over the basic PEP intervention. However, QALY results were not always consistent with other results. In additional economic analyses (Chapter 6) based on data collected during the HIT study (Chapter 2), the results of the primary health outcome selected during the design stage were compared with several other health outcomes, including QALYs. Statistically significant (and clinically relevant) differences between study groups were found on three of the additionally administered clinical outcome measures, but differences were absent for QALY results. The studies presented in this thesis were not designed to assess the validity of QALYs in the context of mental healthcare, and can therefore not lead to conclusions on this topic. In general, it seems advisable to interpret QALY results with some caution in patients with mental illness. As also stated by others (8), economic evaluations should never solely rely on QALYs, but at least carefully consider the results on additional clinical outcome measures as well.

Most economic evaluations conducted in mental healthcare had been designed as cost-effectiveness studies that included single outcome measures aimed at specific aspects of health (5, 6). Using such outcomes could be valid in some situations, for instance when an intervention has a very specific objective and effects are only
expected on a well-defined aspect of health (9). However, for many (economic) studies in mental healthcare this will not be the case, and decision-makers could subsequently be provided with incomplete (and sometimes incorrect) information, as illustrated in Chapter 6. It was suggested to try to aim for the use of instruments assessing overall well-being or Quality of Life (QoL), by means of generic QoL instruments, or otherwise disease-specific QoL instruments. However, in order to allow priority decisions by decision-makers on a broader or even national level, for instance by means of league tables for comparable or related illnesses (10), the same (preference-based) outcome measure has to be applied in all the studies concerned. For advocates of such an approach, it is important to eventually reach consensus among economic analysts and clinicians in the field of mental healthcare on the use of a generic (preference-based) health outcome in economic evaluation. League tables are currently not explicitly used in the decision-making process in the Netherlands, where reimbursement decisions generally concern alternative interventions directly compared in a specific economic evaluation. In the present situation, it seems to be more important that a primary health outcome applied in economic evaluation can reliably assess (changes in) health in specific patient populations, than to enable comparisons across various illnesses or economic studies.

Power analysis and clinical differences between study groups
Due to ethical reasons, power analyses in economic evaluations are usually based on clinical outcomes in the patient population under study, and not on costs (11). Consequently, most economic studies are underpowered to identify statistically significant differences in costs, since the skewed distribution of costs (and high variance) requires larger sample sizes than comparisons of clinical outcomes. For three of the four presented studies (HIT, Cognitive Self-Therapy, PEP), power analyses conducted during the design stage of each study were based on characteristics of outcome measures aimed at specific aspects of health in the patient populations under study. In the fourth study (discontinuation strategy), power analyses focused on utilities from which QALYs were derived. Unexpectedly, in none of the studies could significant differences between groups be demonstrated on the primary health outcome, despite the fact that sample sizes were in accordance with performed power analyses.

There are various possible explanations for the absence of expected significant differences on primary outcome measures. In all the studies, the interventions were compared with CAU as provided by healthcare professionals in the Netherlands. In practice, there appeared to be a large variety in treatments provided under the heading of CAU. Many patients in the CAU conditions received more intensive
treatment than expected, which might explain the smaller differences between CAU and the studied interventions. Furthermore, analyses were mainly conducted in accordance with the intention-to-treat principle, i.e. all patients were included in the analyses regardless of whether they continued in the trial or received the intervention to which they were randomly assigned. This is by many considered to be a justified pragmatic approach for analysing data of trials (12). However, it is most likely to lead to lower estimates of the effect of (experimental) interventions than in more controlled settings, like for instance in pilot studies. In several studies, power analyses were based on information collected in pilot studies, where patient drop-out was limited and practically all the patients received the examined intervention. In a recent paper (13), it was demonstrated that actual effect sizes are commonly overestimated in pilot studies, which may lead to underpowered randomised clinical trials. A careful and more conservative interpretation of the results of pilot studies may lead to better estimates of required sample sizes.

Another aspect that is relevant for the discussion on power analyses and clinical differences concerns the design of a study. All the four studies presented in this thesis were designed as superiority trials. A superiority design is applied when researchers expect to find relevant and significant clinical differences between study groups receiving different interventions or treatments. Alternative study designs are less common for clinical trials, but may be more relevant in some situations (14). When an intervention is expected to be associated with clinical effects comparable to standard treatment, but at the same time may lead to other (economic) benefits, one could consider using a non-inferiority design. Non-inferiority designs intend to show that an intervention is at least equal to an alternative in terms of effectiveness (15). Based on a recent literature overview (16), it seems that a non-inferiority design would be appropriate for (economic) studies on self-help treatments or therapies.

Length of follow-up periods and registration of costs
Follow-up periods of economic evaluations should be long enough to adequately capture relevant consequences of examined interventions. Unfortunately, many economic evaluations conducted in mental healthcare followed patients for only a limited amount of time. For instance, the time horizon of various published economic studies in patients with depression and comorbid anxiety disorders typically ranged from 3 to 8 months (17, 18). Conclusions based on such short study periods should be interpreted with caution, especially since initial positive consequences of psychiatric interventions may diminish over time (19). The follow-up duration of the studies presented in this thesis ranged from 18 (HIT, Cognitive Self-Therapy, discontinuation strategy) to 36 months (PEP). Shorter
follow-up periods would have overestimated either clinical or economic benefits related to the HIT and the Cognitive Self-Therapy intervention, respectively. In the HIT study, there was a statistically significant difference between groups after 9 months on the primary outcome measure in favour of HIT, which was, however, no longer present at 18 months after inclusion. In the study on Cognitive Self-Therapy, healthcare utilisation decreased substantially in both study groups between 6 and 12 months after inclusion, which was most pronounced in the Cognitive Self-Therapy group. However, costs increased again for both groups in the last 6 months of the study. From the current findings, it seems that follow-up periods of at least 12 to 18 months should be used for economic studies in the field of mental healthcare. When focusing on specific symptoms or signs of mental illness expected to occur over a longer period of time, like recurrences or relapses in depression (20, 21), even longer follow-up periods may be indicated.

In all the presented studies, most information on relevant cost aspects was collected by means of a questionnaire, administered to the patients in a face-to-face interview setting. The reliability of information on costs gathered with questionnaires appears to be negatively related to the recall period applied, as suggested by a recent study (22). In that study, it was concluded that recall periods of questionnaires should not exceed the previous 6 months. This was the case for two of the studies included in this thesis. Questionnaires focused on the previous 6 months in the Cognitive Self-Therapy study, and on the previous 3 months in the study on PEP. In the studies on HIT and discontinuation strategy, recall periods were confined to the previous 9 months. Since the questionnaires were administered in an interview setting, the interviewer could provide patients with additional information when needed and could make sure that all the questions were answered. Consequently, there was few missing information when questionnaires could be administered to patients. Furthermore, patients were requested to bring their agenda to the interview (for instance, with information on previous visits to various healthcare professionals) as well as medication prescriptions, which may have had positive consequences for the reliability of cost data collected through patients.

The inclusion and quantification of costs related to productivity losses
All the presented studies were conducted from a societal perspective, i.e. a wide range of costs in and outside the healthcare sector was included in the analyses. This section will specifically focus on costs related to productivity losses. This type of non-medical costs can have a large influence on the total amount of costs in economic studies, also in mental healthcare (23). Over the years, there have been many debates on the inclusion and monetary quantification of productivity losses
due to illness-related absence from work (9). It is widely acknowledged that alternative approaches commonly applied for quantifying productivity losses in economic evaluations may lead to huge differences in estimated costs (24). The human capital approach, for instance, assumes that costs of lost productivity can be estimated by the reduced income of the individual involved. In case of mortality (or permanent incapacity for work), costs are calculated until the retirement age. When using the friction cost method (25), productivity losses are assumed to be confined to the period needed to replace the sick worker. This period is currently estimated at approximately five months in the Netherlands. Not surprisingly, costs of productivity losses are generally much larger when assessed with the human capital approach. It is currently acknowledged that, regardless of the quantification method applied, costs related to productivity losses can be largely overestimated when compensating mechanisms are not taken into account (26). In many situations, for instance, most of the work of people who are (temporary) absent is in practice completed by colleagues during regular working hours. Furthermore, a substantial part of the work can often be compensated by the person involved after returning to work.

In the presented economic evaluations, information was collected on the type of employment, duration of absence, and the return to work after illness-related absenteeism in the patient populations concerned. Results demonstrated that only few patients with chronic schizophrenia (Chapter 2) had paid work, and those who did often worked only for a couple of hours per week in sheltered positions. The number of patients who worked part-time (<35 hours per week) was also considerable in the other studies (Chapters 3-5), where the proportion of patients with paid work who had a part-time job ranged from 60% to 70%. This is in sharp contrast with 35% part-timers in the regular working population (27). Another aspect concerns the return to work after a period of absence. More than half of the patients with schizophrenia and depression indicated that they gradually increased working hours (often over a period of several months) after absenteeism, before working in accordance with contract hours again. In several studies, initial differences between groups were found in the number of patients with paid work, which complicated the interpretation of productivity costs, especially in the study on DRP. Consequently, a conservative approach to the friction cost method was applied, where sensitivity analyses focused on the in- and exclusion of productivity losses. Conclusions based on the results of these sensitivity analyses were generally comparable to conclusions based on the standard economic analyses conducted in each study.

Currently, a study is being conducted in the Netherlands that focuses on the Individual Placement and Support model for vocational rehabilitation in people
with severe mental illness. Costs related to productivity losses will play an important role in the economic evaluation that is part of the study design. An accompanying HTA methodology study will specifically focus on the quantification of productivity losses in this population, which is expected to lead to adjustments of available approaches that could be applied in other mental healthcare studies as well. These adjustments include a more flexible approach towards the period during which productivity losses are quantified.

**Handling missing data in economic evaluations**

Results of longitudinal studies can be biased by missing data due to patients who drop out or are lost to follow-up, especially if their missingness is not completely at random (28). The potential bias related to missing data has now also been acknowledged in the area of economic evaluation (29). Economic evaluations in mental healthcare may be confronted with considerable drop-out of patients, as was for instance the case in several recently conducted economic studies focusing on depression in primary care (30).

Various approaches to account for missing data were applied in the studies combined in this thesis. An example of a simple approach is complete case analysis, in which patients with one or more missing measurements are excluded from the analyses. The correctness of applying this form of analysis largely depends on the type of missingness and the amount of missing data. Longitudinal analyses in the HIT study (Chapter 2) were in accordance with a complete case approach, 17% of the randomised patients for whom at least one of the measurements was missing were excluded from the analyses. In two of the conducted studies (Cognitive Self-Therapy in Chapter 3, discontinuation strategy in Chapter 5), mixed model techniques were used for longitudinal analyses of costs and health outcomes. Mixed model techniques use all available information, i.e. also of patients for whom one or more measurements are missing. In the studies on Cognitive Self-Therapy and discontinuation strategy, cost data was complete for, respectively, 79% and 89% of the included patients. In the PEP study (Chapter 4), missing data posed a particular problem; for less than half of the included patients with depression could costs be assessed at all the measurements. In this study, the expectation maximisation algorithm with a bootstrap approach was applied. This approach is currently considered to be one of the preferred methods for handling missing cost data (31).

When the number of missing data is limited and missingness appears to be completely at random, methods like complete case analysis may still be valid. However, in many situations analysts will have to apply more advanced approaches. Careful examination of the data, with specific attention to the amount
Recommendations for economic evaluations in mental healthcare

Based on the methodological issues discussed above and the findings of the conducted studies, the following recommendations are proposed for future economic evaluations and related research in mental healthcare:

- Cost-effectiveness studies in mental healthcare should apply generic or disease-specific QoL instruments, instead of instruments aimed at specific aspects of health. Various aspects directly related to QALYs, like the validity of instruments from which QALYs are derived, should be adequately assessed in patient populations with mental illness, given current concerns about the use of QALYs in mental healthcare.

- Both the available literature and current findings suggest that in order to perform adequate power analyses, potential effects of interventions should be carefully examined. This is particularly important when using the results of pilot studies. A non-inferiority design seems to be most appropriate for economic studies examining self-help interventions in mental healthcare.

- In order to assess all the relevant economic and clinical consequences of interventions, economic evaluations in mental healthcare should register costs and health outcomes for at least 12 to 18 months. Shorter follow-up periods may lead to incorrect estimations, as indicated by the results of two of the conducted studies. The reliability of cost data could be improved by limiting recall periods of questionnaires to the previous 6 months, or to administer questionnaires on costs by means of face-to-face interviews with the patients, for which patients are requested to bring their agenda.

- Productivity costs can be substantial in mental healthcare and estimates of these costs can vary considerably between commonly applied quantification methods. Initial differences between treatment conditions in the number of patients with paid work may lead to interpretational difficulties, as encountered in this thesis. Based on the current findings, it seems to be highly

and pattern of missingness, will provide the information needed to select adequate methods to deal with the problem that incomplete data may pose in various cost studies, also in mental healthcare.
relevant to provide decision-makers with information on the consequences of in- and excluding costs related to productivity losses.

- Patient drop-out can be considerable in studies in the area of mental healthcare. Especially studies with long follow-up periods and a large number of assessments over time may be confronted with missing data, as was the case for one of the conducted studies. Various approaches to handle missing data are currently available, which will in many situations be more appropriate than complete case analysis commonly applied in the past.

Closing remarks

The increasing (international) awareness of the burden and costs associated with mental illness has resulted in a growing number of economic evaluations and publications in this field of expertise worldwide. The economic evaluations combined in this thesis provided information to support policy decisions in the Netherlands, and subsequently led to positive reimbursement recommendations for two of the four examined interventions (HIT and Cognitive Self-Therapy). In recent years, several studies conducted in other countries have also demonstrated encouraging clinical and economic results of interventions focusing on mental illness. These interventions could prove to be relevant for the treatment of patients in the Netherlands as well. In the UK, for instance, computerised cognitive behavioural therapy is currently recommended as an evidence based, cost-effective intervention in the treatment of patients with mild to moderate depression and anxiety (32). It seems relevant to compare economic aspects of computerised cognitive behavioural therapy with other self-help strategies, like the CST intervention examined in this thesis (Chapter 3). Since there are large differences between countries in the structure of healthcare systems, available regular care, and methods used to assess costs, it is difficult to directly apply results of economic studies conducted in other countries to the situation in the Netherlands, and vice versa. In many cases, detailed (prospective) economic evaluations will have to be conducted in the healthcare system concerned to adequately (re-)evaluate the cost-effectiveness of promising interventions. A recent (model-based) study focused on the economic and clinical consequences of various family interventions in the treatment of patients with schizophrenia in the Australian healthcare system (33). Results suggested that implementation of these interventions in Australia is most likely to be cost-effective. However, it is doubtful whether that will also be the case
for the Netherlands, where family interventions are already more commonly provided by healthcare professionals. Behavioural family treatment was, for instance, one of the treatment options integrated in the HIT intervention described in Chapter 2.

Results from studies that did not find differences between economic aspects of alternative interventions are of scientific importance as well, and may prevent other studies from focusing on topics for which there appears to be little room for economic benefits. Several economic evaluations have recently examined the cost-effectiveness of a wide range of interventions for primary care patients with depression in the Netherlands (30). These interventions included two pharmacy-based approaches, a disease management programme, and Interpersonal Therapy. Results indicated that none of the studied interventions was cost-effective in comparison with regular care provided by general practitioners. Conclusions of these studies are comparable to those of the study on PEP (Chapter 4) that aimed to prevent recurrences in primary care patients with depression. It seems to be difficult to develop interventions for the treatment of depression that are more (cost-)effective than the care currently provided by GPs.

Although the use of atypical antipsychotics is nowadays widely recommended for the treatment of schizophrenia and first onset psychosis, published economic evaluations demonstrate conflicting results when comparing various (a)typical antipsychotics (34). Detailed economic studies with long term follow-up periods are still frequently initiated to examine the economic aspects of various types of medication in chronic and first onset schizophrenia. It may prove to be worthwhile for economic studies on this topic to start focusing more on subgroups of patients that may benefit from specific types of medication. For instance, the study on alternative medication strategies in first onset psychosis (Chapter 5) was unable to find overall differences between guided discontinuation and maintenance treatment. However, a minority of the patients successfully discontinued the use of antipsychotics during the study, without negative economic consequences.

Further implementation of interventions that are proven to be cost-effective is needed to improve the well-being of individuals and to optimise the use of scarce healthcare resources. Unfortunately, the actual implementation of cost-effective interventions in healthcare systems is often complicated (35, 36). The CHOICE programme of the World Health Organization (37) aims to improve the implementation of cost-effective interventions worldwide and illustrates the burden that could potentially be averted. Such initiatives are important in raising awareness among decision-makers about the benefits that can be gained from providing these interventions to patients with mental illness. Presently, the Dutch government stimulates research on various aspects of the implementation of cost-
effective interventions. An ongoing study aims at the implementation of the HIT intervention (Chapter 2) in nine mental healthcare centres across the Netherlands. This study additionally tries to identify factors that may either complicate or facilitate the implementation of new interventions in mental healthcare in general.

To conclude, the relevance of detailed economic evaluations to support policy decisions in the area of mental healthcare seems to be widely acknowledged in the Netherlands nowadays. Various psychosocial and psychopharmacological interventions for patients with mental illness were closely examined in economic studies in the last decade, and economic studies of promising interventions in mental healthcare will remain to be important for decision-making in future years. More (research) attention should be focused on the actual implementation of interventions, which is also stimulated by the Dutch government. The availability of cost-effective interventions needs to be improved, so that both society and patients could benefit more fully from the associated economic and clinical advantages.
References


