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A synthesis of the evidence

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Cost-Effectiveness and Budget Impact Analysis Applied to Specialized Outpatient Psychotherapy for Borderline Personality Disorder in the Netherlands

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Abstract

Background: Specialized outpatient psychotherapy for patients with borderline personality disorder (BPD) is expected to reduce their use of other health care resources. It is currently unknown to what extent the costs of providing these interventions can be expected to be offset by a reduction in other health care costs in the Netherlands. To establish the cost-effectiveness and budget impact of specialized outpatient psychotherapy, the estimated incremental costs are synthesized with the estimated incremental effects. We have developed a method for the synthesis of all relevant evidence on clinical effectiveness as well as health care resource use.

Aim of the Study: The aim of this article is to present a method for the synthesis of evidence for cost-effectiveness and budget impact analysis with a specific application to specialized outpatient psychotherapy for borderline personality disorder in the Netherlands.

Methods: A systematic search of the English-language literature is performed to retrieve evidence on the clinical effectiveness and the health care resource use following 12 months of specialized outpatient psychotherapy for borderline personality disorder. The available evidence is used as an input for a model-based economic evaluation. Simulated patient-level data are used to provide overall estimates of the incremental costs and incremental effects, which

serve to assess the cost-effectiveness and budget impact of specialized outpatient psychotherapy for borderline personality disorder in the Netherlands.

Results: The results indicate that specialized outpatient psychotherapy for BPD can be considered cost-effective and that its scaling up to Dutch national level would require an investment of € 2.367 million (95% C.I.: € 1,717,000 - € 3,272,000) per 1,000 additional patients with BPD. Sensitivity analyses demonstrated the robustness of our findings in light of several uncertain components and assumptions in our calculations, but also their sensitivity to the choice of included studies based on the comparator condition and the assumption of high intervention costs.

Discussion: We present a method for the synthesis of evidence from different types of studies in a way that respects the uncertainty surrounding those findings. Limitations of the study pertain to the inclusion of findings from studies with suboptimal designs, the transferability of research findings, and uncertainty regarding the time horizon considered. More research is needed on the sensitivity of our findings to the choice of included studies based on the comparator condition.

Implications for Health Care Provision and Use: The results suggest that the provision of specialized outpatient psychotherapy for BPD leads to a reduction in other health care resource use. Overall, the results are promising and encourage future studies on aspects that are currently still uncertain.

Implications for Health Policies: The results may support policy makers in deciding whether or not to allocate health care budget for the provision of specialized outpatient psychotherapy for patients with BPD in the Netherlands.

Implications for Further Research: The results provide important directions for future research. This includes the need for future studies to make a comparison between specialized outpatient psychotherapy and treatment as usual and to have longer follow-up time.

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Introduction

Borderline personality disorder (BPD) is a severe mental disorder leading to unstable functioning in the interpersonal, emotional, cognitive and behavioural domains.¹ It has a prevalence of around 1.5% in the general population.² Psychological crises, self-harm and suicide attempts are common in BPD and often result in hospital admissions. Patients with BPD are furthermore known to make extensive use of mental health services when seeking treatment.^{3,4} Therefore, BPD imposes substantial economic costs on national health care budgets. On the one hand, these costs could be alleviated by providing specialized outpatient psychotherapy to patients with BPD; on the other hand, additional costs can be expected for providing such interventions.

For the treatment of BPD, four types of specialized psychotherapy have been found to be effective in reducing BPD psychopathology and symptoms:⁵ dialectical behaviour therapy (DBT),⁶ schema therapy (ST),⁷ mentalization-based treatment (MBT)⁸ and transference-focused psychotherapy (TFP).⁹ Some studies suggest that the costs of providing specialized outpatient psychotherapy are offset by reductions in the costs of other health care services (e.g.^{10,11}). This would imply an overall reduction in health care costs, so that the intervention can be labelled cost-saving from a health care provider's perspective. Since specialized treatments can be assumed to lead to improved health outcomes in addition to potential cost reductions, also their cost-effectiveness is strongly suggested.

An important question is whether this suggestion still holds when taking into account all relevant study findings that are available in the English-language literature. However, we are unaware of any method that has been described to date for synthesizing the available evidence on clinical effectiveness and health care resource use. Importantly, also studies that were not principally designed as economic evaluations provide relevant findings that should be included. These studies often investigate either clinical effectiveness or health care resource use alone. In addition, much relevant evidence has been found in non-controlled studies. The current study aims to present a method for the synthesis of all the available evidence on clinical effectiveness and health care resource use in the English literature in order to assess the cost-effectiveness and the budget impact of specialized outpatient psychotherapy for the Netherlands. The results may support policy makers in the Netherlands in deciding whether or not to allocate health care budget for the provision and upscaling of such interventions.

Methods

Through a systematic search of the English-language literature, we first identified published studies reporting on the clinical effectiveness, health care costs or resource use associated with any of the four types of specialized psychotherapies for BPD. Second, from the studies reporting

on costs or resource use we extracted information regarding the relative change in health care costs following specialized psychotherapy and from the studies reporting on clinical effectiveness we extracted information on changes in health outcomes, or more specifically, the number of quality-adjusted life years (QALYs) gained. Third, the estimated relative change in health care costs was applied to the reference health care costs incurred by Dutch patients with BPD who do not receive specialized psychotherapy to calculate the reduction in health care costs, other than intervention costs, that could be expected following specialized outpatient psychotherapy. Fourth, the reduction in health care costs, other than the intervention costs, following specialized outpatient psychotherapy was compared to the costs of the intervention. Subsequently, we calculated the impact of providing an additional 1,000 patients with BPD in the Netherlands with specialized outpatient psychotherapy on the Dutch national health care budget. Fifth, a synthesis of health care costs and clinical effectiveness was performed to assess cost-effectiveness. A schematic summary of the different steps is provided as a flowchart in **Figure 1**. In an **Appendix** to this manuscript, we provide the mathematical details of the methodology.

Literature Search and Selection Criteria

Since we aimed to synthesize the available evidence on clinical effectiveness and health care resource use or costs, we scrutinized the English-language literature on any of the four types of specialized outpatient psychotherapies for relevant information. Regarding clinical effectiveness, we included studies that report changes in quality of life that were directly measured using the EuroQol-5D (EQ-5D) as well as studies that report changes in depressive symptoms that were measured using the Beck Depression Inventory (BDI). As explained in more detail in the next section, BDI scores were converted to EQ-5D scores on the basis of a mapping function. Regarding health care costs, we limited our analyses to studies on health care costs or health care resource use, as well as studies on the number of inpatient days without reporting other health care use. The last category, although providing an incomplete picture, was included, as inpatient days were considered a major cost driver in patients with BPD.^{11,12} To facilitate comparability between studies, we only included studies primarily aimed at investigating outpatient psychotherapy for BPD. Furthermore, we only included studies in which the patient sample consisted of adults. We searched for relevant literature by checking the references in a Cochrane review on psychotherapy for BPD¹³ and a meta-analysis on DBT for BPD.¹⁴ In addition, we performed a search in PubMed using the search terms [schema OR transference OR mentali* OR dialectical AND borderline AND therapy AND effectiveness]. A search was also performed in the NHS Economic Evaluation Database using the search term [personality disorder OR personality disorders]. The search was deliberately kept broad in order to retrieve all relevant studies. Finally, members of the Guideline Development Group for the development of the Dutch multidisciplinary

PIM WETZELAER ET. AL.

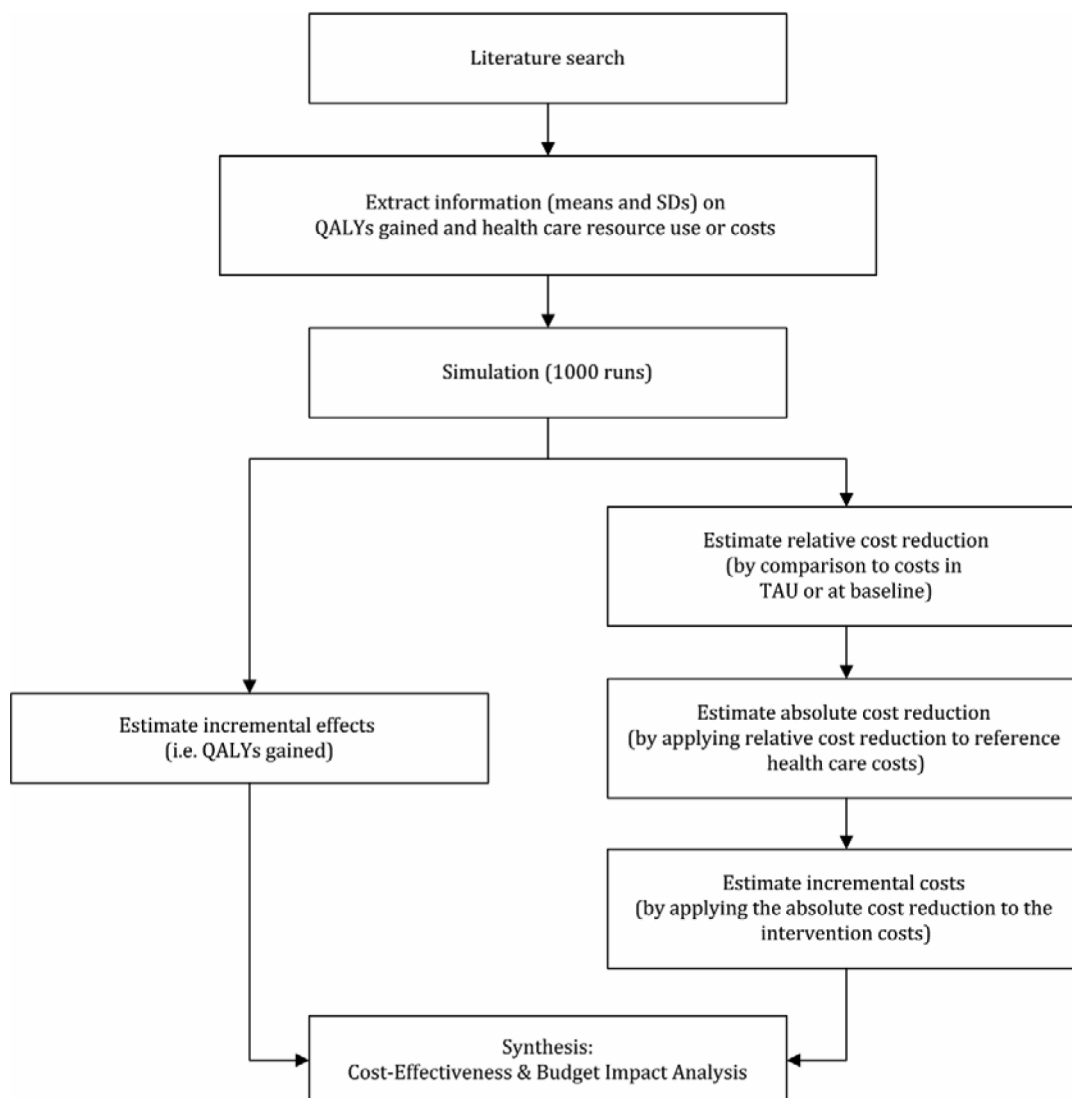


Figure 1. Schematic Summary of the Methodology for this Study.

guideline for borderline personality disorder could contribute studies they deemed relevant for answering the research question. The results of the literature search were reported in a flowchart (Figure 2), in accordance with the PRISMA statement.¹⁵

Information on Health Care Costs and Quality of Life

From the included studies, the mean health care costs (i.e. excluding the costs for outpatient psychotherapy) or resource use over the course of one year of psychotherapy were compared to the mean health care costs or resource use during treatment as usual (TAU). Research designs that include TAU as a comparator condition are considered the ‘gold standard’ in cost-effectiveness research as it allows an assessment of whether experimental treatments have added value for current practice or not.¹⁶ Otherwise, for trials that did not include TAU as a comparator condition, we

compared the mean health care costs or resource use over the course of one year of psychotherapy to the health care costs before psychotherapy commenced (i.e. costs or resource use at baseline). We expressed changes in health care costs as percentages, to take into account the fact that pre-treatment/baseline costs or resource use may differ between studies and countries, thereby enabling the pooling of results from studies using either costs or resource use as outcomes.

For each of the included studies that provided relevant information we also calculated the average improved health outcomes following specialized outpatient psychotherapy. To inform policy makers who decide on health care resource allocation, improved health outcomes need to be measured generically so that they can be compared across various diagnoses. Most often, quality-adjusted life years (QALYs) are used for this purpose in health economic evaluation studies. Therefore, we calculated the average number of QALYs gained of specialized outpatient psychotherapy over the course of one year (for studies in which a comparison was made with TAU, we subtracted the QALYs gained in

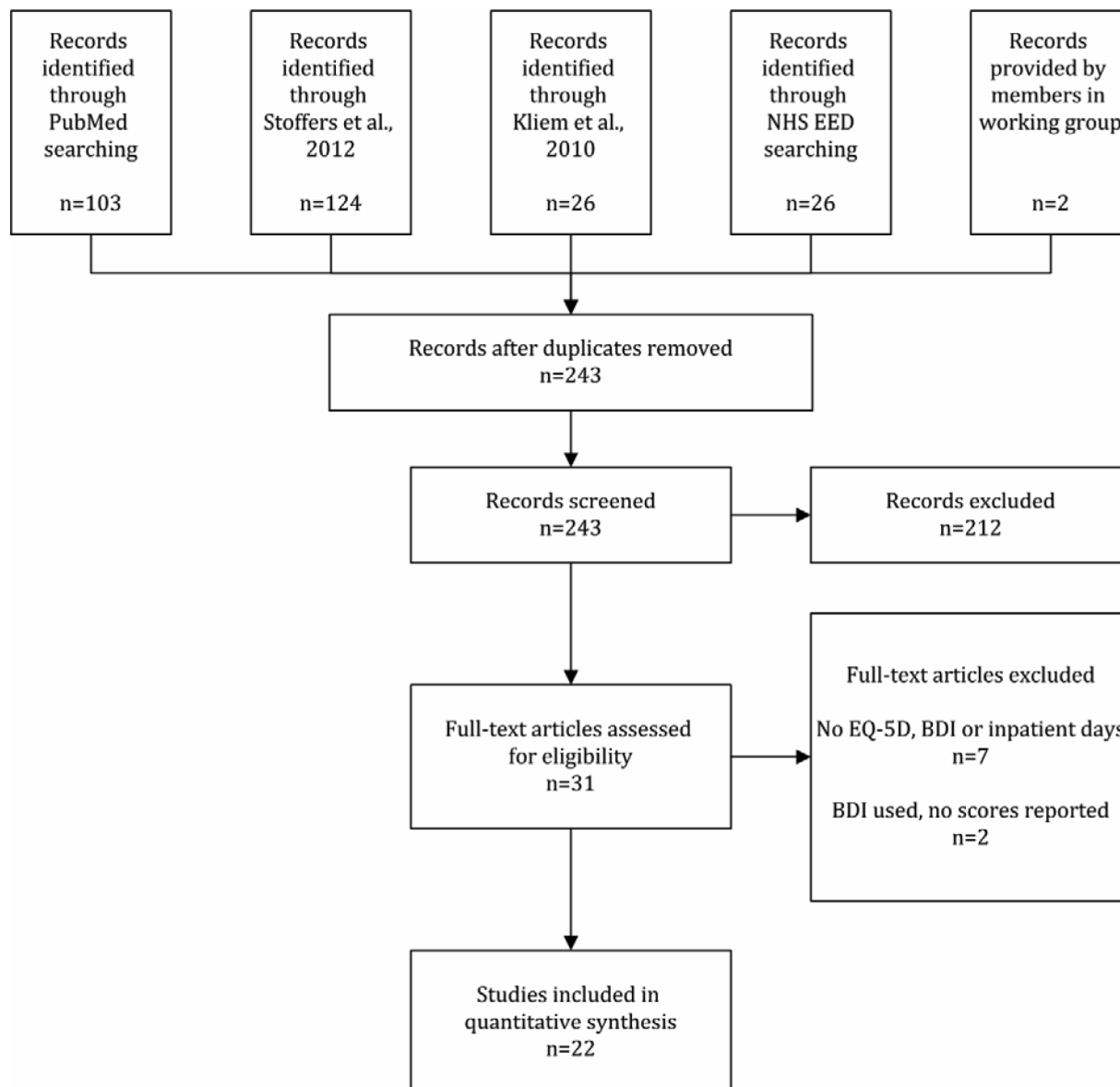


Figure 2. Flowchart of the Literature Search.

TAU from those in the experimental condition). For studies that used the EQ-5D this could be done directly based on EQ-5D scores, for studies that used the BDI instead, the BDI scores were mapped to EQ-5D scores following the mapping function estimated by Brazier and colleagues:¹⁷ EQ-5D score = $1.11 - 0.021 \times \text{BDI score}$.

It was anticipated that only few studies report relevant information for a follow-up time beyond 12 months. Therefore, we considered a time horizon of 12 months. For the included studies that reported the relevant information only for time points earlier than or beyond 12 months, changes in clinical effectiveness and health care resource use were linearly extrapolated or interpolated, respectively.

Intervention Costs

Intervention costs were based on the costs of DBT, because 180

this form of psychotherapy was investigated in most of the included studies. Moreover, we consider this a conservative approach because, in comparison to the other forms of specialized psychotherapy, DBT comprises several components in addition to the individual sessions (and therapists' consultation meetings). DBT consists of four elements: individual sessions, group sessions for skills training, telephone availability of the therapist and therapists' consultation meetings. We calculated the weighted (by sample size) average of the number of individual and group sessions attended reported in studies in which DBT was delivered in its original form according to the manual of Linehan⁶). Since it is the number of sessions actually attended that brings about clinical effectiveness, the calculation of the real-world intervention costs was based on this number and not on the number of sessions prescribed per protocol. We also calculated average costs for telephone

PIM WETZELAER ET. AL.

availability and consultation meetings based on studies reporting this information.

Cost Valuation

All costs, including the reference health care costs (i.e. costs incurred over a 12 month time period by Dutch patients with BPD who do not receive specialized psychotherapy), were indexed to 2015 euros, by using consumer price indices from the Dutch bureau of statistics. The Dutch standard cost prices¹⁸ were used for the valuation of health care resource use in studies that reported the use of other health care resources in addition to inpatient days, and for the calculation of the intervention costs.

Simulation

For each of the included studies we simulated patient-level data for both the relative cost reductions and QALYs gained. The mean and standard deviation of the health care costs or resource use over a period of 12 months of psychotherapy in each study served as inputs for the parameters of gamma distributions. From these distributions, random draws were taken in a number equal to the original study sample size. To estimate the relative cost reductions, these values were compared with the health care costs or resource use over a period of 12 months of TAU when available or pre-treatment/ baseline costs otherwise. The mean and standard deviation of the number of QALYs gained over 12 months in each study served as input parameters for normal distributions. From these distributions, random draws were taken in a number equal to the original study sample size. For each simulation run, an overall weighted (by sample size) mean relative cost reduction and an overall weighted mean number of incremental QALYs were calculated. Finally, in a probabilistic sensitivity analysis the simulation was repeatedly performed for 1,000 simulation runs to estimate the confidence intervals for the mean relative cost reductions and the mean incremental QALYs.

Cost-effectiveness and Budget Impact

The estimated relative reduction in health care costs, apart from intervention costs, was applied to the 12 months' reference health care costs of patients with BPD in the Netherlands who do not receive specialized outpatient psychotherapy. Subsequently, by subtracting the absolute reduction in costs in the Netherlands from the additional costs of providing the interventions, the incremental costs of providing an individual Dutch BPD patient with specialized outpatient psychotherapy were calculated.

To assess the cost-effectiveness of specialized outpatient psychotherapy, the incremental costs and incremental effects (i.e. the number of QALYs gained) were synthesized. For each pair of costs and effects (CE-pair) from the 1,000 simulation runs, the costs per QALY gained were compared with the willingness-to-pay for one QALY by calculating the net monetary benefits.¹⁹ If on average a QALY is gained for

the same amount as or less than the willingness-to-pay for one QALY, then the investment can be considered cost-effective. The probability of cost-effectiveness is shown in a cost-effectiveness acceptability curve (CEAC), presenting the willingness-to-pay values on the x-axis and the probability of cost-effectiveness on the y-axis.²⁰ The estimates for both the number of QALYs gained and the incremental costs resulting from each simulation run are displayed in a cost-effectiveness plane (CE-plane), yielding a cloud of 1,000 costs-effects (CE) pairs.

To assess the budget impact of scaling up the intervention to a national level, adequate information is needed on (i) the total number of patients with BPD in the Netherlands, (ii) the proportion of Dutch patients with BPD who seek help, (iii) the proportion of Dutch patients with BPD already receiving specialized outpatient psychotherapy, and (iv) the proportion of Dutch patients with BPD eligible for the intervention (e.g. see ²¹ and ²²). Unfortunately, information on these aspects is not available to our knowledge. For illustrative purposes, we calculated the budget impact of providing specialized outpatient psychotherapy to an additional 1,000 patients with BPD in the Netherlands based on the incremental costs. Although the exact number of additional patients with BPD to be treated with specialized outpatient psychotherapy after upscaling remains to be determined, we still considered it useful to perform the budget impact analysis following the abovementioned strategy and using the inputs that are available in order to demonstrate the feasibility of our approach.

Cost Perspective

For both the cost-effectiveness and the budget impact analysis, a health and social care system perspective was used. Hence, only health care (including social services) resource use was considered whereas other (societal) costs (e.g. productivity losses and informal care) were not. When evidence is synthesized for the specific purpose of performing a budget impact analysis, the health and social care system perspective is indeed recommended.²¹ However, for a cost-effectiveness analysis a societal perspective is recommended. We anticipated that the availability of literature on studies reporting societal costs is limited.²³ Therefore, also for the cost-effectiveness analyses, a health and social care system perspective was used. The results of our cost-effectiveness analyses are therefore limited to the health and social care system perspective.

Sensitivity Analyses

In addition to the probabilistic sensitivity analysis described, we performed the following one-way deterministic sensitivity analyses to assess the influence of several uncertain components and assumptions in our calculation on the results obtained: analyses using either the lowest and highest estimate for the reference health care costs, an analysis for which only those studies that compare specialized outpatient psychotherapy to TAU were included (to address issues concerning the internal validity of

Table 1. Studies that Provided Information on Costs or Resource Use, Their Characteristics and the Relative Change in Health Care Costs.

Study	N	Type	Comparison	% Health care costs relative to TAU or baseline
Heard, 2000 ¹⁰	22	DBT	TAU	22.52
Turner, 2000 ²³	12	DBT-oriented	Pre-Post	16.76
Clarkin <i>et al.</i> , 2001 ²⁴	23	TFP	Pre-Post	53.68
Brassington & Krawitz, 2006 ²⁵	10	DBT	Pre-Post	70.59 ¹
Comtois <i>et al.</i> , 2007 ²⁶	23	DBT	Pre-Post	33.45
Prendergast & McCausland, 2007 ²⁷	11	DBT	Pre-Post	56.81 ¹
van Asselt <i>et al.</i> , 2008 ²⁸	44	ST	Pre-Post	37.66
van Asselt <i>et al.</i> , 2008 ²⁸	42	TFP	Pre-Post	44.44
Bateman & Fonagy, 2009 ²⁹	71	MBT	Pre-Post	9.06
McMain <i>et al.</i> , 2009 ³⁰	90	DBT	Pre-Post	28.86
Carter <i>et al.</i> , 2010 ³¹	38	DBT	TAU + waiting list	107.59 ¹
Doering <i>et al.</i> , 2010 ³²	52	TFP	TAU ²	44.05
Pasieczny & Connor, 2011 ³³	40	DBT	TAU + waiting list	45.36 ¹
Feigenbaum <i>et al.</i> , 2012 ³⁴	25	DBT	TAU	80.40
Nadort <i>et al.</i> , 2012 ³⁵	62	ST	Pre-Post	29.21 ³
Priebe <i>et al.</i> , 2012 ³⁶	40	DBT	TAU	67.29
Stiglmayr <i>et al.</i> , 2014 ³⁷	47	DBT	Pre-Post	4.42
Wagner <i>et al.</i> , 2014 ¹¹	47	DBT	Pre-Post	26.22

Abbreviations: DBT = dialectical behaviour therapy, ST = schema therapy, TFP = transference focused psychotherapy, MBT = mentalization based treatment, TAU = treatment as usual.

Note: ¹These studies were conducted over a six months' time period, the relative change in health care costs was therefore multiplied by two to estimate the expected change over 12 months. ²In this study, TAU was given by experienced community psychotherapists. ³For this study only the healthcare costs incurred over a three year follow-up time period were reported, these were therefore divided by three to estimate the expected change over 12 months.

uncontrolled studies), an analysis including only studies that focused on DBT (to assess the extent to which findings for DBT are comparable to the other psychotherapies), an analysis based on a more conservative estimation of QALYs gained (the number of QALYs gained in each study is reduced by 30%), and analyses that assumed either a reduction or an increase in the intervention costs by 25%.

Results

Literature Search

As shown in **Figure 2**, the literature search yielded 243 records in total. Based on the selection criteria, 22 studies were included. After full-text screening, 7 studies were excluded because no EQ-5D, BDI or number of inpatient days were assessed. Also, 2 studies that did use the BDI were excluded, because no BDI scores were reported.

Health Care Costs

The included studies that provide information on costs or resource use are listed in **Table 1**. For each study the sample size is indicated, as well as which type of psychotherapy was investigated, whether the calculation of the relative health care costs is based on a comparison with TAU or a pre-post comparison and the percentage of health care costs,

excluding the intervention costs, relative to either 12 months of TAU or the 12 months preceding the psychotherapy, incurred over the course of 12 months.

In total, the included studies represent a sample of 699 patients that provide information on health care utilisation. On average (weighted by sample size) the health care costs are reduced to 38.54% (median = 29.21%) of those in TAU or at baseline.

Quality of Life

Included studies that provide information on changes in quality of life (i.e. number of QALYs gained) following 12 months of specialized psychotherapy are presented in **Table 2**. Only two of the included studies made use of the EQ-5D to measure utilities, which were subsequently used to calculate QALYs. In the other studies, changes in quality of life could be estimated by mapping scores on the BDI to EQ-5D scores.

In total, the included studies represent a sample of 526 patients that provide information on changes in quality of life. The weighted average number of QALYs gained is 0.08 (median = 0.09).

Reference Health Care Costs

The sources that were used to estimate the reference health care costs over a 12 month time period of Dutch patients with BPD who do not receive specialized psychotherapy are

PIM WETZELAER *ET AL.*

Table 2. Studies that Provide Information on Changes in Quality of Life, Their Characteristics and the Mean Number of QALYs Gained.

Study	N	Type	Instrument	Mean QALYs gained (SD)
Turner, 2000 ²³	12	DBT-oriented	BDI	0.17 (0.94)
Koons <i>et al.</i> , 2001 ²⁴	10	DBT	BDI	-0.04 (0.83) ^{1,2}
Clarkin <i>et al.</i> , 2007 ²⁵	23	TFP	BDI	0.01 (0.07) ³
Clarkin <i>et al.</i> , 2007 ²⁵	17	DBT	BDI	0.01 (0.07) ³
Prendergast & McCausland, 2007 ²⁶	11	DBT	BDI	0.10 (0.82) ²
Stanley <i>et al.</i> , 2007 ²⁷	20	DBT	BDI	0.15 (1.03) ⁴
van Asselt <i>et al.</i> , 2008 ²⁸	44	ST	EQ-5D	0.03 (0.32)
van Asselt <i>et al.</i> , 2008 ²⁸	42	TFP	EQ-5D	0.09 (0.29)
Bateman & Fonagy, 2009 ²⁹	71	MBT	BDI	0.09 (0.91)
McMain <i>et al.</i> , 2009 ³⁰	90	DBT	BDI	0.20 (0.78)
Nadort <i>et al.</i> , 2009 ³¹	62	ST	EQ-5D	0.13 (0.30)
Doering <i>et al.</i> , 2010 ³²	52	TFP	BDI	0.00 (0.83) ¹
Stiglmayr <i>et al.</i> , 2014 ³³	47	DBT	BDI	0.11 (0.87)
Gregory & Sachdeva, 2016 ³⁴	25	DBT	BDI	0.08 (0.84)

Abbreviations: DBT = dialectical behaviour therapy, ST = schema therapy, TFP = transference focused psychotherapy, MBT = mentalization based treatment, SD = standard deviation, BDI = Beck depression inventory, EQ-5D = EuroQol-5D (5 dimensions).

Note: ¹In these studies a comparison was made with TAU, therefore the number of QALYs gained in TAU were subtracted from those in the experimental condition. ²These studies were conducted over a six months' time period, the number of QALYs gained was therefore multiplied by two to estimate the incremental effects over 12 months. ³SDs for this study were conservatively estimated based upon the highest (excluding Doering *et al.*, 2010 as the mean: SD ratio was very high in this study due to the mean being close to 0) mean: SD ratio found in the other studies. ⁴In this study of six months DBT BDI scores were only available for the assessment at three months, the number of QALYs gained was therefore multiplied by four to estimate the improvements in quality of life over 12 months.

Table 3. Sources Used to Estimate the Average 12 Month Reference Health Care Costs of Dutch Patients with BPD.

Source	N	Mean 12 Months' reference health care costs (in 2015 euros)
Van Asselt <i>et al.</i> , 2008 ²³	86	5,913*
Soeteman <i>et al.</i> , 2008 ⁴	1,740	10,264**
Nadort <i>et al.</i> , 2012 ²⁴	62	4,878
Vektis, 2013	65,718	6,144
Bamelis <i>et al.</i> , 2015 ²⁵	320	12,082
Laurensen <i>et al.</i> , 2006 ²⁶	403	13,492

Notes: *Based on a re-analysis of the data in which only health care costs were taken into account; **Soeteman *et al.*,⁴ report the increase in societal costs specific for BPD in comparison to other personality disorders (PDs). Furthermore, they report that 66.5% of societal costs are health care costs. Therefore, 66.5% of the increase in societal costs for BPD has been added to the average health care costs for all PDs to calculate the average health care costs for BPD.

listed in **Table 3**. For each source the mean health care costs are listed, expressed over a time period of 12 months during which specialized outpatient psychotherapy was not systematically provided, as well as the corresponding sample sizes. These sources include studies that were identified from our literature search^{24,25} or suggested by members of the working group for the development of the Dutch multidisciplinary guideline for personality disorders.^{4,26,27} Additionally the Vektis database was used which contains health care resource use data that is provided by all Dutch health insurers as well as other parties. The Vektis data represent the average health care costs of adult patients with personality disorders (who are diagnosed as such and whose health care costs exceed zero) in the Netherlands. Also included is one study on schema therapy for personality disorders other than BPD to partly compensate for the small

number of studies that provide information on this aspect.²⁶ The reported costs from this study are well in line with the other studies. The weighted (by sample size) average costs equal € 6319.

Intervention Costs

Two studies on DBT, delivered according to the manual of Linehan,⁶ were used for estimating the intervention costs. In the study by McMain *et al.*²⁸ (n=90), patients attended on average 32 individual sessions and 26 group sessions and in the study by Wagner *et al.*¹¹ (n=47) patients attended on average 33.7 individual sessions and 16.9 group sessions. The weighted averages (by sample size) are 32.5 individual sessions and 23 group sessions. Although only little information is available on the costs for providing telephone

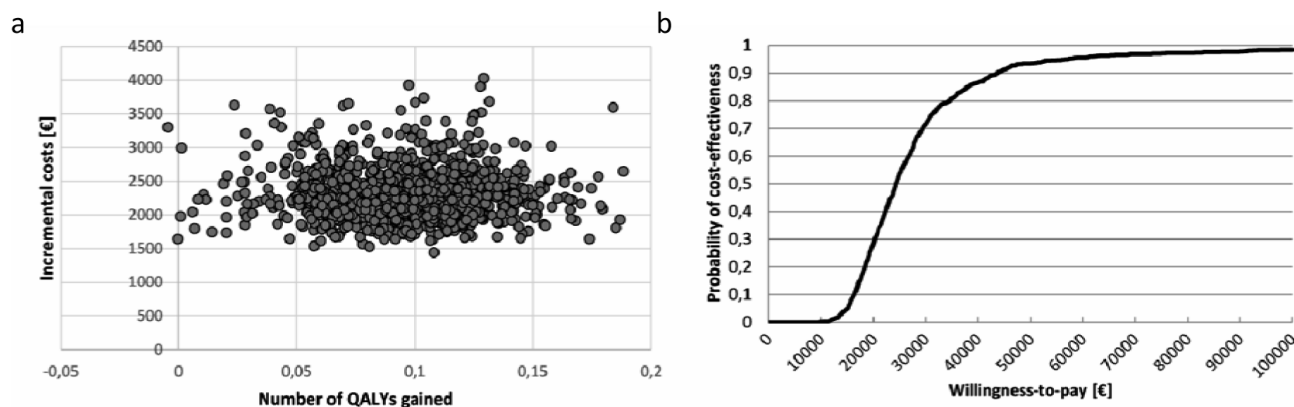


Figure 3. Cost-effectiveness Plane (a) and Cost-effectiveness Acceptability Curve (b) of the Main Analysis.

Notes: The figures are based on 1,000 simulations. In the CE-plane, each dot represents a CE-pair from one simulation.

availability of the therapist and the frequency of therapists' consultation meetings, we assumed that, similar to Wagner *et al.*,¹¹ the costs of these two components equal 26% of the costs for individual and group sessions combined. In total, intervention costs are estimated to be € 6,249.

Cost-effectiveness and Budget Impact

Given an average reduction in health care costs to 38.54% (95% C.I.: 28.27 – 52.88%) of the reference health care costs, when applied to the average reference health care costs of € 6,316, the expected average cost saving following specialized outpatient psychotherapy is € 3,882. Subsequently, the incremental costs for providing such treatment can be calculated by subtracting the reduction in costs from the intervention costs (€ 6,249), which gives € 2,367 (95% C.I.: € 1717 – 3272). Since the weighted average number of QALYs gained is 0.08 (95% C.I.: 0.03 – 0.16), the incremental cost-effectiveness ratio (ICER) for specialized outpatient psychotherapy is € 29,588 (95% C.I. € 13,455 – 75,940) per QALY gained. In figure 3, both the CE-plane (Figure 3a) and CEAC (Figure 3b) of the main analysis are displayed.

At the willingness-to-pay value of € 50,000 considered acceptable for gaining one QALY by the Dutch guideline,²⁹ given the burden of disease of 0.54 for BPD,³⁰ specialized outpatient psychotherapy for BPD has a 94% probability of being cost-effective. To calculate the budget impact of providing an additional 1,000 patients in the Netherlands with specialized outpatient psychotherapy, the incremental costs are multiplied by 1,000, which results in € 2,367,000 (95% C.I.: € 1,717,000 – 3,272,000).

Sensitivity Analyses

In Figure 4, the CEACs from the various sensitivity analyses are presented. In the first sensitivity analysis (figure 4), instead of a weighted average of estimates for the reference health care costs of Dutch patients with BPD who

do not receive specialized outpatient psychotherapy we used the lowest estimate. This decreased cost-effectiveness, so that specialized outpatient psychotherapy has a 83% probability of being cost-effective at a willingness-to-pay value of € 50,000. In a sensitivity analysis in which we used the highest estimate found in the literature for the reference health care costs (not shown in Figure 4), cost-effectiveness is increased to the extent that it has a 98–100% probability of cost-effectiveness over the whole range of willingness-to-pay values. In the second sensitivity analysis (Figure 4), in which we only included studies with a 12 month duration, there was a 96% probability of cost-effectiveness at a willingness-to-pay value of € 50,000. The third sensitivity analysis (Figure 4), for which only studies on DBT were included, produced results that are comparable to the main analysis, with a 94% probability of cost-effectiveness at a willingness-to-pay value of € 50,000. The fourth sensitivity analysis (Figure 4), in which only studies using TAU as the comparator condition were included, demonstrates that the results are sensitive to the choice regarding the inclusion of studies based on the comparator condition that was used. This analysis shows that the probability of cost-effectiveness is then decreased to 21%. When the number of QALYs gained in the included studies was conservatively assumed to be only 70% of what is originally reported, as in the fifth sensitivity analysis (Figure 4), cost-effectiveness is reduced. At a willingness-to-pay value of € 50,000 the probability of cost-effectiveness is 81%. In the sixth sensitivity analysis (Figure 4), that only included studies that used the EQ-5D, there is a 94% probability of cost-effectiveness at a willingness-to-pay value of € 50,000. When the costs of the intervention were assumed to be 25% lower than estimated in the main analysis, cost-effectiveness is increased, as shown in the seventh sensitivity analysis (Figure 4), with a 99% probability of cost-effectiveness at a willingness-to-pay value of € 50,000. Conversely, the eighth sensitivity analysis (Figure 4) shows that increasing intervention costs by 25% decreased the cost-effectiveness so that the probability is 50% at a willingness-to-pay value of € 50,000.

PIM WETZELAER ET AL.

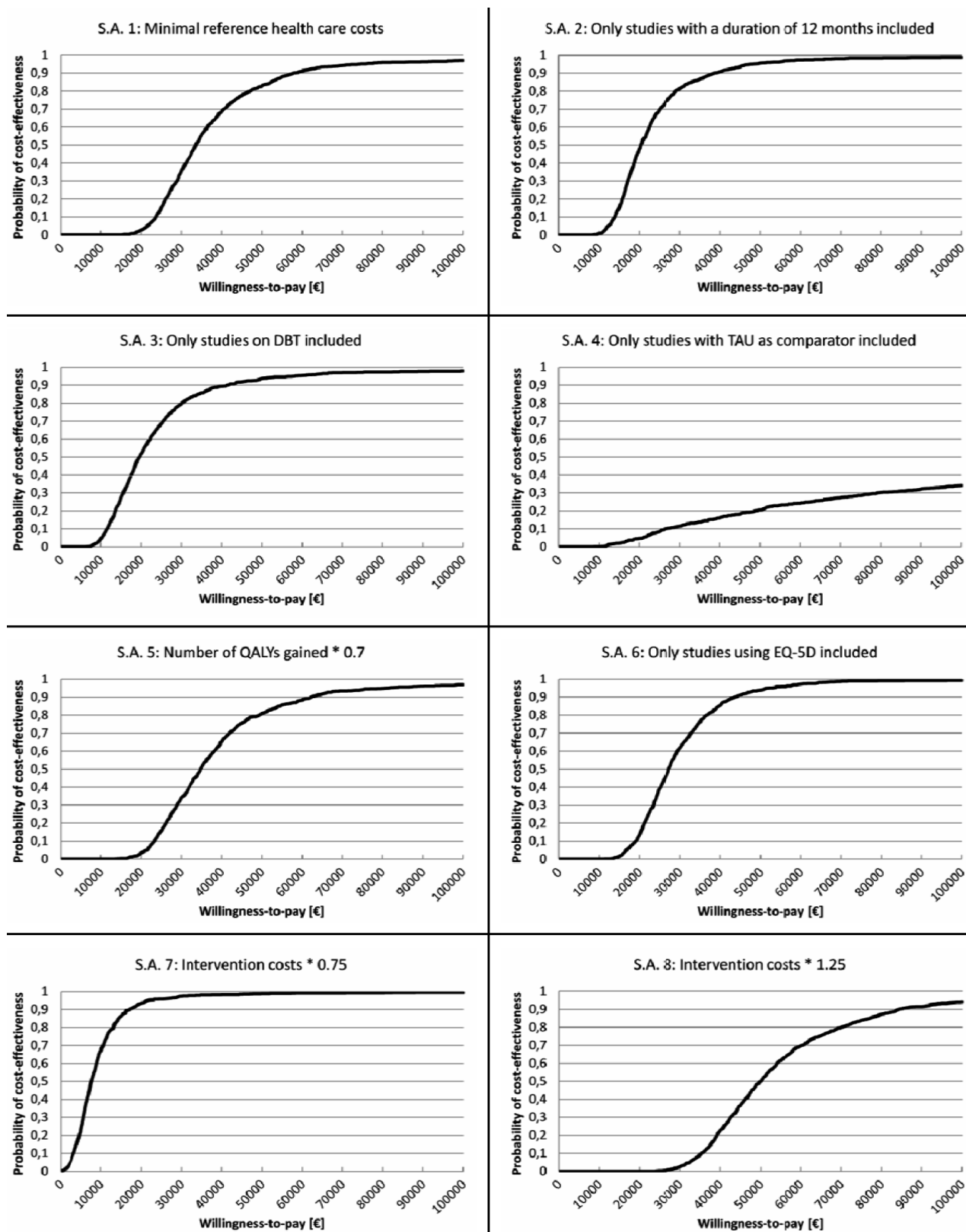


Figure 4. Cost-effectiveness Acceptability Curves for the Sensitivity Analyses.

Notes: From left to right, top to bottom: S.A. 1 = lowest estimate used for reference health care costs; S.A. 2 = only studies with a duration of 12 months were included; S.A.3 = Only studies on DBT were included; S.A. 4 = Only studies with TAU as comparator condition were included; S.A. 5 = number of QALYs gained multiplied by a half for all included studies regarding clinical effectiveness; S.A. 6 = Only studies that used the EQ-5D were included regarding clinical effectiveness; S.A. 7 = 25% reduction in intervention costs assumed; S.A. 8 = 25 % increase in intervention costs assumed.

Discussion

Main Findings

By synthesizing the available evidence on the clinical effectiveness and health care resource use following 12 months of specialized outpatient psychotherapy, our results suggest that these treatments provide good value for money. We have demonstrated that, based on the available evidence, providing specialized outpatient psychotherapy to an additional 1,000 Dutch patients with BPD requires an investment of near € 2.4 million. Taking into account the improved health outcomes following these treatments, the investment needed for up-scaling can be considered cost-effective. The sensitivity analyses demonstrate that our findings are robust to most, but not all, of the alternative approaches to the methodological choices and assumptions that were made.

Strengths and Limitations

In this article, we have presented a method to assess the cost-effectiveness and budget impact of specialized outpatient psychotherapy for borderline personality disorder (BPD) in the Netherlands. The strength of this methodology is that a wealth of information has been incorporated and synthesized to inform policy making in the Netherlands. It has the advantage of incorporating various sources of empirical evidence: from both the clinical as well as the health economic research fields, from study designs that include, but are not limited to, RCTs, and from studies conducted in different countries. It further presents a way of pooling the parameter uncertainty found in the results from various studies. From the evidence available in the English-language literature, we estimated the overall average relative reduction in health care costs and applied this to the average reference health care costs of patients with BPD in the Netherlands. The incremental costs were calculated by subtracting the estimated reduction in health care costs from the intervention costs. We also estimated the incremental effects as the overall average number of QALYs gained based on the available evidence in the international literature. The incremental costs and incremental effects were synthesized to assess the cost-effectiveness and the incremental costs were further used to analyse the budget impact for the up-scaling of specialized outpatient psychotherapy for BPD in the Netherlands.

This study also has its limitations. To assess reductions in health care resource use following specialized outpatient psychotherapy we have taken into account studies that as a minimum reported on the number of inpatient days, because these are assumed to be major drivers of health care costs in patients with BPD.^{11,12} Since this type of information is often reported in articles in which the main focus is on clinical effectiveness, an advantage of our approach is that more studies could be included than if we had only included studies reporting a full health care cost analysis or health economic evaluation. However, we have also included other health care resource use where possible. It can be argued that

the extent to which inpatient days are indeed major drivers of health care costs may differ between countries. Furthermore, the extent to which reductions in inpatient days are also exemplary for reductions in the use of other health care resources has not been currently investigated.

Ideally, studies on outpatient psychotherapy are designed to have an adequate follow-up time period to reveal the full impact of the intervention, including both clinical as well as health economic parameters. Unfortunately, this is not the case for many of the studies on psychotherapy for BPD. For this reason, the time horizon for the analysis performed in this article has been limited to one year. For the studies that were included that only considered a six month time period findings were linearly extrapolated to one year, thus assuming that no ceiling effects occurred within the next six months of time. For the study by Nadort,²⁵ which had a duration of three years, total health care costs were divided by three, thus assuming that for this study costs increased linearly over time. A sensitivity analysis was performed to assess the influence of these assumptions, which only included studies with a duration of 12 months. The results of this analysis were comparable to the main analysis, thereby demonstrating the robustness of the latter.

Another limitation is that only two of the included studies directly measured changes in quality of life using the EQ-5D. Therefore, also studies were included that used the BDI as a measure for depressive symptoms, as BDI scores could be converted to EQ-5D scores by using a mapping function. Obviously, there is not a one-to-one correspondence between the impact of depressive symptoms and BPD symptoms on quality of life, thereby making the validity of this conversion procedure questionable. Nonetheless, owing in particular to its focus on the subjective experiences and cognitions in depression, which also play an important role in BPD (although they are qualitatively different than in Major Depressive Disorder), the BDI is considered to be sensitive in patients with BPD.^{31,32} In a sensitivity analysis, we included only those studies that measured changes in quality of life directly using the EQ-5D. The results of this analysis are well in line with those from the main analysis. In another sensitivity analysis, we reduced the number of QALYs gained in each study by 30%. Even with this conservative approach, specialized outpatient psychotherapy still has an 81% probability of cost-effectiveness for a willingness-to-pay value of € 50,000, which is the threshold for disorders with a burden of disease similar to BPD in the Netherlands.

A further drawback is that not all of the included studies were RCTs with TAU as a comparator to the experimental condition. The advantage of RCTs is that they have high internal validity, so that differences between treatment conditions can be causally attributed to the actual treatments that patients received. The choice for TAU as an appropriate comparator condition is motivated by the need for establishing whether the treatment under investigation has added value for the current practice or not. To assess the extent to which the inclusion of studies that were not RCTs or did not use TAU as the comparator condition, we have performed a sensitivity analysis that only included studies that did have TAU as a comparator condition. In contrast to the main analysis, this

PIM WETZELAER *ET AL.*

analysis does not support the cost-effectiveness of providing a larger number of patients with BPD with specialized outpatient psychotherapy. However, a number of factors should be considered that could explain the discrepancies between this sensitivity analysis and the main analysis, in addition to the above-mentioned concerns relating to internal validity. First, there is only very little evidence available from studies comparing specialized outpatient psychotherapy for BPD with TAU: only two studies regarding the clinical effectiveness (representing only 62 participants in total) and six studies regarding health care resource use were included that used TAU as a comparator condition. Second, both studies on the clinical effectiveness were based on the BDI (similar to most of the included studies; see above). Therefore, to gain better insight into the sensitivity of our results to the choice of included studies based on the comparator condition used, more research is needed.

In addition to gaining better insight into how specialized outpatient psychotherapy as a whole compares to TAU, the future availability of more studies that compare a specific type of specialized outpatient psychotherapy with TAU would also open new methodological avenues. For example, (Bayesian) network meta-analyses could then be used to explore how the different types of specialized outpatient psychotherapy compare to each other. At present, we considered the available evidence too scarce for the application of this method. This relates to the fact that there is currently only little evidence available for specialized outpatient psychotherapy other than DBT and that there are only a few studies that compare a specific type of specialized outpatient psychotherapy to TAU or another specific type of specialized outpatient psychotherapy.

A cautious approach was taken to deal with the uncertainty surrounding the intervention costs. In our study, the intervention costs were based on the costs of DBT, as this form of psychotherapy is the most comprehensive one (i.e. consisting of the most different components) of all four forms of psychotherapy considered and was therefore also assumed to be the most costly. We have performed sensitivity analyses in which the intervention costs were varied both by + and – 25%. The results of the first indicate that with increased intervention costs, specialized outpatient psychotherapy has a 50% probability of cost-effectiveness for a willingness-to-pay value of € 50,000. This demonstrates that our findings are sensitive to alternative assumptions involving particularly high intervention costs. Future research on comparisons between the different types of specialized outpatient psychotherapy as well as studies that focus on the added value of specific components of psychotherapy could help to identify the most cost-effective therapeutic approach and format of delivery. When the intervention costs are assumed to be lower, cost-effectiveness is enhanced compared to the main analysis. We furthermore performed a sensitivity analysis in which only studies on DBT were included, since DBT was the type of psychotherapy that was most often investigated. The results of this analysis are similar to the main analysis, thereby demonstrating that the main analysis is robust against the inclusion of other types of specialized psychotherapy in our investigation.

Ideally, our investigation should be based on a large number of studies that have simultaneously investigated both the effectiveness and costs of specialized outpatient psychotherapy. This would also provide the empirical evidence on the basis of which the correlation between incremental costs and incremental effects can be quantified. However, given the limited availability of such studies, it was decided to include studies that have investigated either effectiveness or costs. It is thus a limitation of our study that we did not take into account the possible correlation between incremental costs and incremental effects. As a consequence, the real-world incremental costs and incremental effects would presumably be slightly different than in our simulation. Another limitation pertains to the possible bias that may be present in combining the findings of those studies that have investigated either effectiveness or costs. This is because when only the effectiveness of psychotherapy is investigated, the possibility exists that researchers have put extra effort into maximizing the effectiveness, thereby increasing intervention costs. Vice versa, when only costs are investigated, there might be an inclination towards keeping the costs to a minimum, possibly at the expense of the effectiveness of psychotherapy.

We included several sources in our investigation to determine the reference health care costs of patients with BPD in the Netherlands who do not receive specialized outpatient psychotherapy. There was substantial variability in findings regarding these reference health care costs. Therefore, in addition to the main analysis that was based on a weighted (by sample size) average, we have also performed sensitivity analyses that were based on both the lowest and highest reference health care costs. Although cost-effectiveness logically increases as these reference costs are assumed to be higher (i.e. higher reference costs leave more room for cost reduction than lower costs), even when based on the lowest costs, specialized outpatient psychotherapy for BPD can still be considered as cost-effective.

In general, our investigation is characterized by substantial uncertainty. The primary aim of the study however, is to illustrate a method that allows us to make the most of the available evidence. By making conservative choices wherever possible and by assessing the influence of several uncertain components and assumptions in various sensitivity analyses, our findings are useful for two reasons. First, they will help to determine how, based on the evidence that is currently available, specialized outpatient psychotherapy will have an impact on the Dutch health care budget and to what extent investments in these treatments can be considered cost-effective. Second, they provide important directions for future research. For example, when the results of a sensitivity analysis deviate substantially from the main analysis for reasons that remain largely unknown (e.g. as is the case for the sensitivity analysis that only included studies using TAU as a comparator), studies could be designed to specifically address this.

An issue that is pivotal to any synthesis of international evidence for producing country-specific estimates is related to the transferability of research findings. Indeed, a limitation of this study pertains to the fact that it is unknown to what

extent the findings from one country are transferable to another. As mentioned before, we assumed inpatient days to be the major drivers for health care costs in BPD, but the extent to which this holds true may differ between countries. In a wider sense, this applies to country-specific estimates of any particular kind of health care resource use. One step towards a resolution of this transferability issue would be to try and map out the variations between different countries by performing future studies in a multinational context. Once the variations are estimated, adaptations of research findings may possibly be devised to enhance their transferability. Although in this study we estimated the cost-effectiveness and budget impact of specialized outpatient psychotherapy specifically for the Netherlands, our methodology could, quite straightforwardly, be applied to other countries as well. To make a case for other countries, both for the reference health care costs as well as for the intervention costs, country-specific data are needed.

One final aspect of uncertainty in the context of our investigation that should be mentioned is the extent to which our findings apply to longer time periods than the one year that is currently considered. The improvements in health outcomes following specialized outpatient psychotherapy may persist over time, during which no further treatment is needed. In that case, since the investment has already been made, then also the reductions in health care costs will continue to accrue over time. The cost-effectiveness of specialized outpatient psychotherapy will then be enhanced for as long as there is no additional need for receiving further treatment. However, to demonstrate such effects over longer time periods in a way similar to our current approach, more empirical evidence is needed from studies that employ a longer time horizon for follow-up. It would be particularly interesting to validate the findings from our current investigation with those from a large-sample RCT performed in the Netherlands, preferably with a long time period for follow-up, and preferably with TAU as a comparator condition.

Despite the limitations described above, we have demonstrated an approach that allows the synthesis of all relevant study results that are available, be they from clinical studies or health economic investigations, and from RCTs as well as non-controlled trials, in a way that respects the uncertainty that surrounds those findings and will help to shed light not only on the cost-effectiveness and the budget impact per se, but also on which remaining questions could be addressed in future studies. The results from our investigation may support policy decisions about the allocation of health care budget for the provision of specialized outpatient psychotherapy for borderline personality disorder patients in the Netherlands.

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Appendix

Incremental Effects

For each study 1, 2, ..., i , we perform j number (corresponding to the study sample size n_i) of random draws $e_{i,1}, e_{i,2}, \dots, e_{i,j}$ from the Normal distribution $N(\mu_i, \sigma_i^2)$, where μ_i and σ_i^2 are the mean and variance, respectively, of the number of QALYs gained during 12 months of specialized outpatient psychotherapy in study i . Subsequently, we calculate an overall, weighted by sample size, mean number of QALYs gained E , following:

$$\Delta E = \frac{\sum_{i=1}^i \bar{e}_i * n_i}{\sum_{i=1}^i n_i}.$$

This procedure is replicated in 1,000 simulation runs to provide the range of values for the incremental effects E from which we calculate the mean and 95%-confidence intervals and which are synthesized with the incremental costs.

Incremental Costs

For each study 1, 2, ..., i , we perform j number (corresponding to the study sample size n_i) of random draws $c_{i,1}, c_{i,2}, \dots, c_{i,j}$ from the Gamma distribution $\Gamma(\alpha_i, \beta_i)$, where α_i and β_i are the shape and rate parameters, respectively, for the distribution of the health care costs incurred during 12 months in study i . The values for these parameters can be calculated from the mean μ_i and standard deviation σ_i ,

following $\alpha_i = \left(\frac{\mu_i}{\sigma_i}\right)^2$ and $\beta_i = \frac{\sigma_i^2}{\mu_i}$. Subsequently, we calculate the overall, weighted by sample size, mean incremental costs C , following:

$$\Delta C = C_I - \left(\frac{\sum_{i=1}^i \sum_{j=1}^j \frac{c_{i,j}}{C_{C,i}}}{\sum_{i=1}^i n_i} \right) * C_R,$$

where $C_{C,i}$ are the health care costs in TAU or at baseline used for comparison for study i , C_R are the reference health care costs, and C_I are the intervention costs. Also this procedure is replicated in the 1,000 simulation runs to provide the range of values for the incremental costs from which we calculate the mean and 95%-confidence intervals and which are synthesized with the incremental effects.

Synthesis

The incremental effects and incremental costs are synthesized by calculating the incremental net monetary benefits (INMBs), following $INMB = \lambda * E - C$, where λ is the willingness-to-pay value.¹ In each of a 1,000 simulation runs, one pair of incremental effects and incremental costs are synthesized in this way and by tracking the relative number of simulation runs in which $INMB > 0$ the probability of cost-effectiveness is estimated for the range of different willingness-to-pay values λ .

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