Cognitive Behavioural Therapy for psychosis: a cost-effectiveness study using the EPiSODe model

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CBTp: cost-effectiveness using the EPiSODe model

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Abstract

Background: Cognitive Behavioural Therapy for psychosis (CBTp) is an effective psychological treatment for Schizophrenia Spectrum and other psychotic Disorders (SSD). Despite guidelines recommending CBTp for all psychotic disorder patients, many SSD patients lack access to the treatment and little is known about its long-term cost-effectiveness. The aim of this study is evaluating the cost-effectiveness of CBTp for the treatment of psychotic disorders through scenario analysis from a healthcare perspective.

Methods: Increased implementation of CBTp was evaluated using a real-world SSD population (N = 12,835) from the northern Netherlands (2010-2019). A patient level model was used to simulate the long-term effects of rehospitalisation rate. We compared treatment as usual (TAU) with the same TAU plus hypothetical CBTp for all individuals not having received such in TAU, hence patients who received any CBTp sessions prior were excluded (N=2,679). Outcomes considered were quality adjusted life years gained and total costs of mental healthcare. Additional sensitivity and scenario analyses were performed to evaluate structural and parameter uncertainty.

Results: TAU+CBTp was a cost-effective treatment in 61.2% of the simulations. The simulated net present values for QALY gains were 0.038 and for incremental costs were €492 per patient on average, resulting in an expected incremental cost-effectiveness ratio (ICER) of €12,947.

Conclusions: The evaluation shows that CBTp is likely a cost-effective treatment, although results were uncertain. These findings stress the importance of sufficient availability of CBTp for SSD patients. Making CBTp available for all eligible SSD patients may lead to substantial health gains for the SSD population and cost savings from the healthcare perspective in The Netherlands.

Keywords: cost-effectiveness, cognitive behavioural therapy, psychotic disorders, discrete event simulation model, scenario analysis.

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Introduction

Schizophrenia Spectrum and other psychotic Disorders (SSD) have a relatively low prevalence, yet are highly burdensome from both the patient's and the societal perspective [1-4]. These disorders severely impair the quality of life (QoL), functioning, and social participation of patients [4-7]. Treating SSD is often challenging, considering that more than half of the patients do not respond adequately to current treatments [8, 9]. The main treatment options for patients with SSD are antipsychotic medication combined with psychological treatment [10, 11].

Cognitive Behavioural Therapy for psychosis (CBTp) is an effective psychological treatment for SSD patients [12-18]. CBTp aims to reappraise the meaning and purpose of hallucinations and delusions to reduce distress and improve coping in daily life [19]. To this end, CBTp focuses on a collaboration between patient and therapist, in which they create a personalized case formulation to achieve the patient's goals and to increase control over symptoms and problems, improving autonomy and self-esteem [20]. According to the National Institute for Health and Care Excellence (NICE) and various (inter)national guidelines, among which the Dutch guideline [21], CBTp is an essential treatment and should be offered to everyone with a psychotic disorder [21-26]. Specifically, the Dutch care standard for psychosis states that CBT should be offered to all patients experiencing subclinical psychotic symptoms, psychotic symptoms, and affective symptoms [27].

A recent report by the Dutch Association of Behavioural and Cognitive Therapy (VGCt) highlighted that only 20-25% of the patients who should have been offered CBTp were estimated to have access to the treatment [28]. To improve quality of CBTp in current practice, more psychologists are needed, and psychologists need more specific training [28]. Internationally, clinical practice is also not in line with guideline recommendations [29-32].

Clinical trials and meta-analyses have shown that CBTp improves positive symptoms [16-18, 20, 33], reduces negative symptoms [18, 33, 34], and improves short-term functioning [35] of SSD patients. Less is known on long term health benefits. Recent meta-analyses found no or small significant effects of CBTp on Quality of Life (QoL) for SSD patients [36-38]. Two meta-analyses have shown that CBTp

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reduces relapse and rehospitalisation rates, although the uncertainty range around the estimates was large. One meta-analysis reported the relative risk (RR) for relapse based on rehospitalisation (RR = 0.70, CI 0.54 to 0.91 [10]), the other meta-analysis reported the relative risk of rehospitalisation (RR = 0.79, CI 0.60 to 1.04 [38]). Both meta-analyses had follow-up times of at most 24 months. Underlying trial populations primarily consisted of individuals with schizophrenia and schizoaffective disorder, with occasional inclusion of other psychotic disorders such as delusional disorder and brief psychotic disorder, with positive symptoms sometimes used as inclusion criteria. To get insight into long-term cost-effectiveness, data synthesis using a simulation model is needed.

A systematic review by Jin et al. [39] showed that the majority of cost-effectiveness studies for SSD evaluated antipsychotics, and often used low-quality simulation models. Another systematic review, by Shields et al. [40], showed that the cost-effectiveness of CBTp interventions for psychotic disorders was mostly evaluated in terms of improved functioning (improvement on Global Assessment of Functioning: Haddock et al. [41]; additional days of normal functioning: van der Gaag et al. [35]). Only one study investigated the incremental health benefits in terms of quality adjusted life years (QALYs), but this was a trial based study with a total N of 77 and a time horizon of 9 months, only evaluating the cost-effectiveness during the intervention period [42]. Since the systematic review by Jin et al., another simulation study investigated the cost-effectiveness of CBTp for Ultra High Risk individuals [43]. Hence, as of yet, no simulation studies have investigated the effects of CBTp on reduced rehospitalisation or relapse rates and taken a long-term perspective on cost-utility of CBTp.

In order to demonstrate the need for proper implementation of this intervention in current clinical practice, we aim to show the potential long term cost utility of CBTp using simulation modelling. A thorough scenario and sensitivity analysis was performed to deal with the substantial uncertainty around the existing evidence for the effectiveness of CBTp on health related quality of life (HR-QoL) and healthcare use related outcomes. Based on these analyses, we aim to draw conclusions about the cost-utility of implemented CBTp for SSD patients from the healthcare perspective. To assist readers without a background in health economics, the online supplementary document (Appendix A) includes a glossary of key health economic terms.

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Methods

A patient-level state transition model was used to simulate the long-term effects of CBTp on Specialized Mental Healthcare (SMH) via the relapse rates. Lower relapse probability leads to less cumulative time in states with reduced HR-QoL and therefore more time is spent in better health states, also reducing healthcare needs. This model, the Evaluating Psychosis by Simulating Outcomes for Decision support (EPiSODe) model, has been validated and is more extensively described on our Open Science Foundation page https://osf.io/k56sp/?view_only=5c1753079c44440cb73fc931aed255e5.

Effect sizes and uncertainty ranges for the relapse and rehospitalisation rates, and HR-QoL utility weights corresponding to model states were based on published literature. Further model parameters were estimated from routine care data from SMH in the northern Netherlands over the period 2000 to 2019. The initial 10 years of data were used to create a baseline population, while the following 10 years of data were used for internal validation of the model. Scenarios with and without full implementation of CBTp were compared and sensitivity analyses performed.

Study sample

Administrative registry data with basic patient characteristics (age, sex, and diagnosis) and detailed healthcare use (both in- and outpatient care recorded on a daily basis) were available for (N = 12,835) SSD patients receiving SMH in the north of the Netherlands. The catchment area consisted of the provinces Groningen, Friesland, and Drenthe, and the four major SMH providers in this area collected the data. All diagnoses were established by qualified psychologists and psychiatrists in a clinical setting, using the DSM-IV criteria, and were available to select SSD patients for the purposes of this study (more information in Appendix B). Unless they actively avoid care, SSD patients will be treated in SMH.

Model

Healthcare use trajectories were simulated using a patient-level continuous-time state transition model for SSD. This model distinguishes three healthcare use states representing “in-episode”, “out-of-episode”, and death. The “in-episode” state is defined as a period of increased use of specialized

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mental healthcare, and distinguishes between episodes with inpatient care and episodes with only outpatient care. The “out-of-episode” state is defined as a period of decreased healthcare. Within this framework, “relapse” is defined as the transition from out to in-episode, while “remission” is defined as the reverse. Mortality was modelled as a transition from either the ‘in-episode’ or the ‘out-of-episode’ state to an absorbing ‘death’ state, using parametric distributions estimated with the available data [44]. The time horizon used was ten years.

Intervention and comparator

For the purposes of the current study, CBTp was defined as a psychological intervention, based on Dutch guidelines [21]. This involved a minimum of 16 sessions of individual therapy provided by a qualified practitioner, with each session assumed to last approximately one hour. Patients who have been identified to have received treatment were excluded from the study sample, resulting in a sample of patients that did not receive CBTp. This sample of patients was used in the simulation model.

We compared treatment as usual (TAU) with the same TAU plus hypothetical CBTp for all individuals not having received such in TAU. For TAU we simulated actual healthcare use and QALYs for the selected patient population and time frame. For TAU+CBTp, we repeated this with increased one-time treatment costs as a result of CBTp and adjusted sojourn times. The adjusted sojourn times were based on the reduced rehospitalisation or relapse rates resulting from the hypothetical CBTp treatment. The differences in simulated costs and QALYs estimated the long-term effect of providing a proper CBTp treatment to all patients.

Costs

Treatment costs were calculated as the hourly wage rate of the practitioner times the duration of the therapy in hours. The number of therapy sessions was set to 16 with a cost of €108.22 per session (total treatment costs of €1731.52 per patient). By assumption, CBTp did not incur severe adverse effects. Other costs, such as travel costs or additional education costs per patient for medical practitioners (e.g. resulting from a required course or obtaining a qualification) were assumed as negligible for the purposes of the current simulation study. Unit costs were obtained and indexed for 2019 and determined using the Dutch costing manual [45].

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At each iteration, the simulation model uses cost-equations to assign a level of costs for each patient based on their current model state, modelled sojourn time, and other patient characteristics. Transitions to the episode state lead to an increase in costs, while transitions to the out-of-episode state imply a cost-decrease. In this way, individual patients will differ in the level of costs, reflecting the large variation in intensity and type of care provided to Schizophrenia patients. In principle, as the simulated patients are assumed to transition less frequently to the “in-episode” state after receiving CBTp, these patients use less costly SMH.

Health effects

The effectiveness of CBTp on rehospitalisation rates was estimated as a relative risk, based on two reviews [10, 38]. The duration of this treatment effect was conservatively assumed to be two years, which was the maximum follow-up time of the underlying randomized controlled trials (RCTs). In sensitivity analyses, we varied the treatment effect duration from 1 to 10 years.

Long term health benefits were estimated in QALYs gained by keeping track of the total time in episode with outpatient care, the total time in episode with inpatient care and the total time in a stable out of episode state and multiplying each with their respective health related quality of life weight (Table OS1 in the Online Supplement). HR-QoL weights were taken from a review by Zhou J et al. [46]. The utility values estimated by Briggs et al. [47] based on a Time Trade-off (TTO) instrument were chosen to be the most recent and suitable HR-QoL weight estimates for our model states. These estimates have also been used in existing cost-effectiveness studies for antipsychotics [48-50]. In line with existing cost-effectiveness studies for antipsychotics with similar states, the HR-QoL value for the in-episode with outpatient care state was estimated as the average QoL value of the two other (best and worst) states, while the largest observed standard error was used to model uncertainty. Base case estimates from the patient sample were selected as a conservative assumption (see Table OS1 in the Online Supplement).

Model simulations resulted in total QALYs and total costs for the simulated population for each scenario, per year. These were used to calculate net present values, using a discount rate of 3.5% for

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both costs and QALYs as per the UK guideline [51]. In a scenario analysis, a discount rate of 4% for costs and 1.5% for QALYs was used as per the Dutch guidelines [52].

Finally, the intervention was considered as being cost-effective if the Incremental Cost Effectiveness Ratio (ICER) did not exceed a Willingness To Pay (WTP) threshold of €50,000 [53].

Sensitivity analyses

One-way sensitivity analyses were used to investigate the importance of the model assumptions concerning treatment effect duration, hourly medical practitioner costs, number of treatment sessions, group therapy (reduced treatment costs p.p.), discount rates, HR-QoL weights and direct QoL improvements. The results were presented in Tornado diagrams. Furthermore, a probabilistic sensitivity analysis was performed, using 750 outer loops and 250 inner-loops (using the method from Oakley et al. [54] to determine these values). Parameters varied in the PSA and their distributions are presented in Table OS2 in the Online Supplement. Constant random seed (Common Random Numbers (CRN)) was used in each pair of simulation comparisons as a variance reduction technique.

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Results

Descriptive statistics for the study population and sample after exclusion criteria are shown in Table 1.

[Table 1]

Table 1: Overview of the study sample. Individuals may have had multiple primary diagnoses over the course of the study period.

The cost-effectiveness plane for the base case scenario with parameter uncertainty is shown in Figure 1. In around a third of the simulations, TAU+CBTp was the dominant treatment with both cost savings and health gains relative to TAU. Assuming a WTP threshold of €50,000 [53], TAU+CBTp was found to be cost-effective in more than 60% of the simulations. The cost-effectiveness acceptability curve is also shown in Figure 1. For a WTP of €80,000, TAU+CBTp would be cost-effective in more than 70% of the simulations.

[Figure 1]

CE = Cost-effectiveness; WTP = Willingness to pay; QALY = Quality adjusted life year.

Figure 1: Left: cost-effectiveness plane. Dots represent outer loop draws (parametric uncertainty). WTP line = €50,000 per QALY gained. Right: Cost-effectiveness acceptability curve (CEAC).

Table 2 shows the mean results for various scenario analyses. One such analysis is determining the expected additional costs and health benefits for different assumptions on treatment effect duration. The scenario with the shortest treatment duration (1 year) shows a mean simulated 0.031 QALY gain and €2410 in costs per patient for TAU+CBTp compared with TAU. The scenario with the longest treatment duration (10 years) shows a mean simulated 0.061 QALY gain and €1163 in costs per patient for TAU+CBTp compared with TAU.

Another analysis shows the impact of using the lower rehospitalisation risks resulting from the meta-analysis by McDonagh et al. [10]. Lower rehospitalisation risks would lead to reduced costs, and a larger health benefit, as shown by this scenario. Using the lay-person sample to determine TTO QoL

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weights would result in larger health benefits. Finally, we observe that a higher discount rate for costs leads to a lower net present value of cost savings, while the discount rate barely affected the health benefits.

[Table 2]

Table 2: Overview of expected cost, QoL differences, and ICER resulting from CBTp treatment, sensitivity analysis assuming different scenarios.

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Discussion

Use of CBTp is likely a cost-effective treatment for SSD patients. Following our base case analysis, TAU+CBTp was the dominant treatment relative to TAU in more than 30% of the simulations, and cost-effective in more than 50% of simulations. On average, the simulated QALY gain was 0.038, approximately two weeks in full health, and the simulated costs were €492 per patient, which were then more than covered by cost reductions as a result of less healthcare use episodes. For patients in the Netherlands this could result in an expected QALY gain of 3157 years for an expected cost of €40.9 million euros. The probability that CBTp is a cost-effective treatment increased with longer treatment effect duration, larger treatment effect, and cheaper treatment.

In line with existing literature, we found that the incremental health benefits for CBTp were relatively small. However, our study also showed that the potential cost savings of proper CBTp implementation could be substantial. To the best of our knowledge, only two studies by Barton et al. [42] and by Jin et al. [43] investigated the cost-effectiveness of CBTp using QALYs as the health benefit outcome. Both studies showed that CBTp could be a cost-effective treatment for psychosis patients. However, Barton et al. did not consider the preventive effect of CBTp on rehospitalisation chance. Moreover, the study by Barton et al. was based on a small trial sample, while we simulated a large population with a long follow-up time. Compared to Barton, our results showed a larger probability of CBTp being a cost-effective treatment. The study by Jin et al. considered people at high risk for psychosis, in contrast to our study which evaluated CBTp in patients with existing diagnosis. Their study showed that CBTp could be cost-effective at preventing onset of the disorder, while we showed that CBTp could be cost-effective for preventing recurrent healthcare use relapses.

Other studies that investigated the cost-effectiveness of CBTp, did not use QALYs, but a variety of short-term outcome measures which makes it impossible to compare results directly. Studies by Haddock et al., van der Gaag et al., and others [34, 35, 41, 55] have shown that CBTp could improve functioning and (both positive and negative) symptoms in addition to reducing relapse risks, further supporting the benefits of CBTp.

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A major strength for the current study was the availability of administrative healthcare use and diagnosis data for a large population of SSD patients in the Northern Netherlands. The patients in our study data were the vast majority of SSD patients in the study catchment area, which was beneficial for the representativeness of our study sample. Furthermore, follow-up was available between 2000 until 2019. As a result, we were able to mitigate the issue of left-censoring by splitting the data in 2010, using the initial 10 years of data to create a baseline population while another 10 years of data was available for internal validation of the model.

By using a state-transition simulation model, we were able to perform a wide range of scenario and sensitivity analyses. To verify the robustness of our findings, we included uncertainty around regression model coefficients, the rehospitalisation risk, and QoL weights in the PSA. Furthermore, we performed additional analyses with varying assumptions on treatment costs, with parameters extracted from different available meta-analyses, and investigated the impact of alternative QoL weights based on input from a lay-person sample.

A major limitation of simulation modelling using administrative data is the difference between simulated reality and the real world. Reality is inherently more complex than a simulation, and assumptions in the model are generally based on estimations which could be biased or even incorrect. Moreover, estimations performed in small samples or trials could have substantial uncertainty, such as the parameter values used for rehospitalisation risk. Moreover, while the lack of qualified practitioners is the primary barrier to CBTp availability [28], suggesting that missing out on treatment is largely random. However, treatment effect sizes extracted from the literature may be overly optimistic if patients most likely to benefit have been prioritised for treatment and thus excluded from the study [56]. Another limitation of our study is the reliance on the assumption that CBT-p effectiveness is consistent across all subtypes of SSD, primarily because the available trials providing evidence are conducted mostly with schizophrenia patient populations. This assumption was made because the target population includes all patients experiencing subclinical psychotic symptoms, psychotic symptoms, and affective symptoms [27]. While this assumption may not hold for patients with a substance-related psychosis diagnosis, such patients comprised less than 5% of the study population, meaning their exclusion would have minimal impact on our findings.

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Since the total number of patients in multiple RCTs included in the meta-analyses was small [38], we recommend that future RCTs consider the inclusion of QoL or rehospitalisation related outcomes as primary or secondary endpoints in their studies. Another factor affecting the uncertainty around effect sizes is the quality of the CBTp treatment. Duration of the treatment [57], in addition to education level, type, and competence of the medical practitioner also affect treatment outcomes and effect size uncertainty [58-61]. Furthermore, the primary focus of the treatment has been mentioned as a reason for varying effect sizes per outcome [62, 63]. Additionally, various effect sizes are reported to vary over time after treatment [10].

Another point to consider is the feasibility of adding CBTp to TAU in practice. For instance, when a major reason for lack of available treatment is lack of available practitioners, then providing additional CBTp may come with the cost of reducing other beneficial treatments [64]. Such real-world implications are not captured by the model and are beyond the scope of the current study. Enhancing indication practices may be a key aspect of the solution, as findings indicate that CBTp is not cost-effective for a portion of patients, and other findings support the notion that CBTp is not effective for everyone [65-67].

The current study shows the potential of more widespread use of CBTp and hence indicates it might be worthwhile to indeed assure better availability of practitioners to offer CBTp to those who need it. Since the effectiveness of CBTp varies between patients, perhaps the cost-effectiveness could be further improved by applying a more personalized approach, considering evidence summarized by Newman-Taylor and Bentall hints that relatively small effect sizes mask heterogeneity of treatment outcomes [56].

Moreover, various cost and health differences were not considered in the simulation study. After considering potential societal cost savings such as reduced informal care, and other positive health benefits such as improved functioning or symptoms [68], the treatment could be found to be even more cost-effective relative to our analysis where we merely consider the potential effect on rehospitalisation. Although psychosocial interventions such as CBTp could sometimes have harmful

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effects [69], there is a lack of direct evidence that CBTp leads to a significant increase of severe adverse events [38, 70], hence our assumption to omit modelling of such adverse events.

In conclusion, CBTp is likely a cost-effective treatment, with a 61.2% probability of being cost-effective at a WTP of 50.000 euro per QALY and using conservative assumptions about health benefits of CBTp. These findings show the importance of sufficient availability of CBTp for SSD patients. Proper implementation of and guideline adherence for CBTp could lead to substantial health gains and cost savings for the SSD population in the Netherlands. Further clinical investigation of QoL-effects and in particular the effect on risk of relapse or rehospitalisation would be required to reinforce these findings.

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Declarations

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Conflicts of interest

The authors declare that there are no conflicts of interest in relation to the subject of the study.

Author contributions

SK, MB, EV, JM, TF and RB contributed to the study conception and design. Data preparation was performed by EV and SK. Analyses were performed by SK. The first draft was written by SK and MB. All authors were involved in subsequent versions of the manuscript. All authors have read and approved of the final manuscript.

Ethics statement

The study was based on pseudonymized administrative healthcare data for which no ethical approval was needed.

Transparency declaration

All authors and guarantors declare that the manuscript is an honest, accurate, and transparent account of the study being reported. No aspects of the study have been omitted.

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Availability of data and material

The data used in this research concerns linked pseudonymised patient level data, suitable for use by researchers, after permission from the members of the IMPROVE consortium. However, due to binding legislation and institutional policy sharing of these data to third parties is not possible.

Code availability

The code for this project is publicly available on the Open Science Framework (OSF) at https://osf.io/k56sp/?view_only=5c1753079c44440cb73fc931aed255e5.

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Table 1: Overview of the study sample. Individuals may have had multiple primary diagnoses over the course of the study period.

Variable	Study population N = 12,835	CBTp exclusion N = 10,156
Male %	7447 (58.0%)	5990 (58.6%)
Age on entry, Mean (SD)	38.8 (17.0)	40.4 (17.4)
Follow-up time in years (2010-2019), Mean (SD)	8.1 (2.6)	8.0 (2.6)
Number of episodes (p.p.), Mean (SD)	3.6 (2.8)	3.8 (2.7)
Episode duration in years (p.e.), Mean (SD)	0.2 (0.8)	0.2 (0.9)
Total cost (p.p.), Mean (SD)	€33,736	€28,371
Cost per follow-up year, Mean (SD)	€4836	€4359
Primary diagnosis (DSM-IV)		
-291 (Alcohol related), N (%)	79 (0.6%)	68 (0.6%)
-292 (Drugs related), N (%)	567 (4.4%)	444 (4.3%)
-293 (Medical condition), N (%)	102 (0.8%)	83 (0.8%)
-295 (Schizophrenia), N (%)	6299 (49.1%)	4912 (48.0%)
-297 (Delusional disorder), N (%)	1156 (9.0%)	930 (9.1%)
-298 (Brief / other psychosis), N (%)	5672 (44.2%)	4323 (42.3%)
-Missing (Unknown), N (%)	682 (5.3%)	620 (6.1%)

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652 **Table 2: Overview of expected cost, QoL differences, and ICER resulting from CBTp treatment,**
653 **sensitivity analysis assuming different scenarios.**

654

Scenario		Expected cost difference	Expected difference in QALYs	ICER
Base case		€492	0.038 years	€12,947
Treatment effect duration	**2 year (base)**	€492	0.038 years	€12,947
	1 year	€705	0.030 years	€23,500
	3 year	€272	0.043 years	€6,326
	5 year	€-98	0.052 years	Dominant
	10 year	€-566	0.061 years	Dominant
Rehospitalization risk	**0.79 (0.60-1.04) (1)**	€492	0.038 years	€12,947
	0.70 (0.54-0.91) (2)	€428	0.051 years	€8,392
QOL weight	**Patient sample (base case) [46]**	€492	0.038 years	€12,947
	Lay person sample [46]	€492	0.046 years	€10,696
Discount rate	**3.5% Cost, 3.5% outcome (base case)**	€492	0.038 years	€12,947
	4% Cost, 1.5% outcome	€506	0.038 years	€13,315

655

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657 plus standard care versus standard care for people with schizophrenia. Cochrane Database of
658 Systematic Reviews. 2018; (12).
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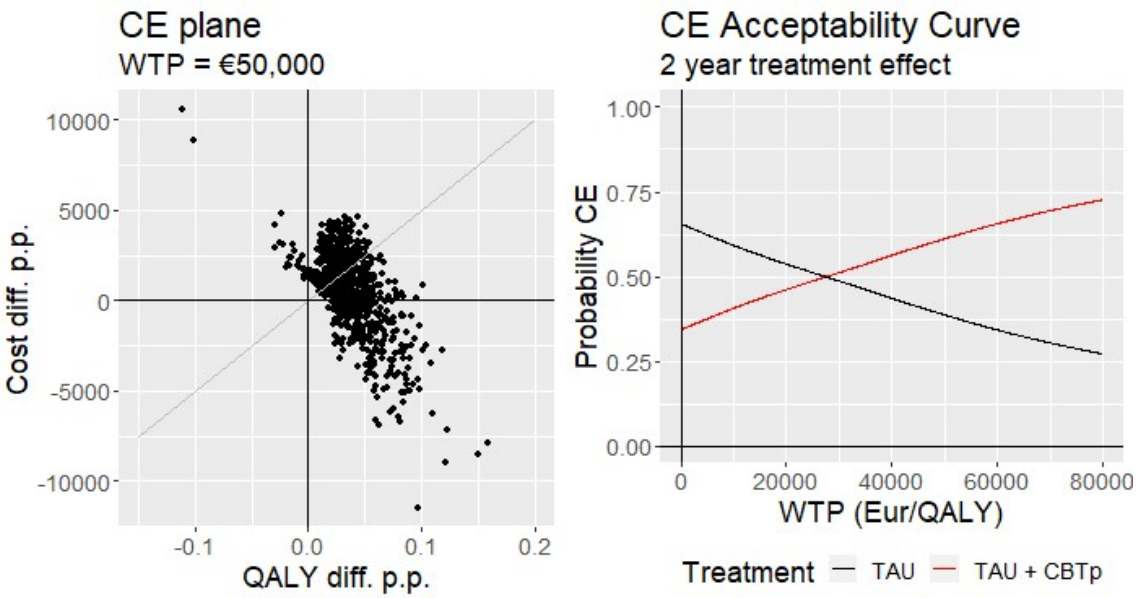
661 **Figure 1**



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