COST-UTILITY OF COLLABORATION MODELS IN MENTAL HEALTH CARE



Maartje Goorden

Cost-Utility of Collaboration Models in Mental Health Care

MAARTJE GOORDEN

Lay Out: M. Goorden
Cover design: Fenna Schaap
Printed and published by: Proefschriftmaken.nl | www.proefschriftmaken.nl

©2018 M. Goorden
All Rights Reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior written permission the author.

Cost-Utility of Collaboration Models in Mental Health Care

Kostenutiliteit van Collaboration Models in de Geestelijke Gezondheidszorg

Proefschrift

ter verkrijging van de graad van doctor aan de

Erasmus Universiteit Rotterdam

op gezag van de

rector magnificus

Prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

20 September om 13:30 uur

door Maartje Goorden

geboren te Sittard

Erasmus University Rotterdam



Promotiecommissie:

Promotoren:	Prof.dr. C.A. Uyl-de Groot
	Prof.dr. C.M. van der Feltz-Cornelis
Overige leden:	Prof.dr. W.J.G. Hoogendijk
	Prof.dr. J.J.V. Busschbach
	dr. H.W.J. van Marwijk
Copromotor:	dr. L. Hakkaart-van Roijen

CONTENTS

1 Background 1
1.1 Allocation of patients 1
1.2 Cost- effectiveness in mental health 2
1.3 Innovative interventions and collaboration 5
1.4 Aim and Research Objectives 6
1.5 Outline of this thesis 7
2 Developing a decision tool to identify patients with personality disorders in need of highly specialized care 11
2.1 Introduction 13
2.2 Methods 15
2.3 Results 21
2.4 Discussion 32
3 Cost utility analysis of a collaborative care intervention for major depressiv e disorder in an occupational healthcare setting 45
3.1 Introduction 47
3.2 Methods 49
3.3 Results 53
3.4 Discussion 58
4 Cost- utility of collaborative care for major depressive disorder in primary care in the Netherlands 61
4.1 Introduction 63
4.2 Methods 66
4.3 Results 71
4.4 Discussion 80
5 Cost-utility of collaborative care for the treatment of comorbid major depressive disorder in outpatients with chronic physical conditions. A randomized controlled trial in the general hospital setting (CC-DIM) 85
5.1 Introduction 87
5.2 Methods 89
5.3 Results 94
5.4 Discussion 104
6 Cost utility analysis of a collaborative stepped care intervention for panic and generalized anxiety disorders in primary care 109
6.1 Introduction 111
6.2 Methods 113

6.3 Results 118
6.4 Discussion 123
7 The cost-effectiveness of family/family-based therapy for treatment of externalizing disorders, substance use disorders and delinquency: a systematic review. 129
7.1 Introduction 131
7.2 Methods 133
7.3 Results 136
7.4 Discussion 160
8 Cost-effectiveness of multidimensional family therapy compared to cognitive behavioral therapy for adolescents with a cannabis use disorder: Data from a randomized controlled trial 165
8.1 Introduction 167
8.2 Methods 169
8.3 Results 174
8.4 Discussion 183
9 Discussion 189
9.1 Part 1: Allocation of patients 189
9.2 Part 2: Collaboration between settings 189
9.3 Part 3: Interventions based on collaboration 191
9.4 Limitations 191
9.5 Clinical recommendations and research implications 194
9.6 Policy implications 195
9.7 Final remarks 196
10 Summary 197
11 Samenvatting 199
12 PhD portfolio 203
13 About the author 207
14 Dankwoord 209
15 References 211

1 BACKGROUND

Mental disorders are common, affecting 1 out of 4 adults every year in the European population [1] and include a wide range of conditions described in the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) [2]. Anxiety disorders, insomnia, depression, somatoform disorders and alcohol and drug dependence have the highest prevalence [1]. Besides their high prevalence, mental disorders have a large burden of disease and are the main contributor to chronic conditions for the population of Europe. The World Health Organization (WHO) estimates that 7.4% of the Disability Adjusted Life Years (DALYs), which is a combination of number of life years lost and number of years lived with a disability (YLD), is caused by mental and behavioral disorders [3]. When compared to other chronic diseases, these disorders also rank high on YLD. Common mental disorders like chronic depression, alcohol disorders and anxiety disorders are positioned first, third and sixth on this scale [4]. Their high prevalence, burden and chronicity attribute to high societal expenses. The mean cost per patient per year for common mental disorders is €3,200 [5]. Out of these costs, 85% is attributed to productivity losses [5]. In light of these high costs and the existing scarcity in resources due to increasing costs and limited budget, there is a growing interest in methods to distribute resources efficiently.

1.1 ALLOCATION OF PATIENTS

To increase efficiency in resources of mental healthcare, firstly the identification process of patients to mental healthcare interventions should be optimized. In contrast with other parts of health care, like oncology or cardiovascular diseases, validated tools for patient stratification in psychiatric practice are missing [6]. In absence of validated tools, clinicians currently rely on overall clinical impression or severity of symptoms and as a consequence, patients may not receive appropriate treatment. In Western countries only half of the patients with severe mental disorder get treatment and in case of receiving treatment, treatments are often not appropriate or don't fulfill the minimal standards for adequate treatment according to available evidence-based guidelines [7]. In less developed countries the numbers are even lower. In the Netherlands, GPs are responsible for treating patients with milder forms of mental illness in primary care and can refer people

who are more seriously ill to specialized mental healthcare services. Primary care is provided in the family physician practice, the occupational physician office and general hospitals. It is defined as "the provision of integrated, accessible health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained partnership with patients, and practicing in the context of family and community." [8] Specialized mental health care is intended for patients with serious and complex psychiatric disorders and is provided in specialty mental health institutions and by psychiatric wards in a general hospital setting. Treatment of more serious and complex psychiatric disorders sometimes requires highly specialized care. In the study of Krugten et al. (2017) [9] highly specialized care is defined as specialized interventions delivered by highly-trained staff with specific expertise in a given field to individuals with problems that cannot be treated with sufficient result by either primary or specialized mental health services. The settings provide treatments which differ in respect to their intensity; primary care ranks the lowest and highly specialized care the highest. Patients with more severe and complex disorders should be referred to higher intensity settings compared to patients with less severe and complex disorders. In Fig. 1.1, a flow diagram provides an overview of the referral process. Early stratification of more complex and severe patients with evidence based-decision tools for the appropriate setting of care is expected to lead to a reduction in costs and decrease loss of quality of life, as it may reduce the number of treatment steps.

1.2 COST-EFFECTIVENESS IN MENTAL HEALTH

In the three settings of care, various treatments may be applied. For policymakers, it is important to have knowledge about the differences between cost and benefits of these treatments. This information can support decisions regarding the reimbursement of these treatments. For this purpose economic evaluations are used.

Common types of economic evaluations are cost-effectiveness analysis (benefits are expressed in clinically relevant effect measures) and cost-utility analysis (benefits are expressed as quality-adjusted life years (QALYs)). In cost-effectiveness studies an innovative intervention is compared to (most ideally) usual care. When comparing these interventions, not only the effects are taking into account but also the costs by estimating the price for one unit of clinical

improvement. This is called the incremental cost effectiveness ratio (ICER). In theory, any disease specific clinical outcome measure can be used to determine the ICER, however, in this way it is not possible to compare the outcomes across mental disorders. Additionally, it can result in meaningless outcomes, as there is no threshold for the ratios of these outcomes. Cost-utility analysis (CUA) was developed to overcome this problem.

In a CUA the health benefits of a technology are typically expressed in QALYs as measured by the EQ-5D [10]. This instrument consists of five dimensions (self-care, usual activities, pain/discomfort, and anxiety/depression) and it combines length and quality of life in one utility, ranging from 1 (perfect health) to values below 0 (worse than dead). In the 3-level version of the EQ-5D each dimension consists of the levels: no problems, some problems and extreme problems, therefore defining a total of 243 different health states. These health states can be linked to empirical valuations of the Dutch general public, allowing utilities to be computed. To obtain the QALYs, the area-under-the curve method (AUC) can be applied [11].

In the past, there has been some concern about the validity of the EQ-5D in capturing clinical effects. However, a recent study [12] showed that for common mental disorders in adults, the instrument can be used with some confidence. However, in case of schizophrenia the EQ-5D seemed to be less appropriate [12].

The costs in mental health care can be estimated by the Treatment Inventory Cost in psychiatric patients (TiC-P) questionnaire. This instrument is used to collect data on healthcare consumption and productivity losses for patients with a psychiatric disorder [13]. Part 1 of the TiC-P is a validated instrument that measures the number of contacts with health care services during the last 3 months. We can extract the healthcare costs by multiplying them by the reference unit prices of these services. The second part of the TiC-P contains the Short Form- Health and Labour (SF-HLQ). This part assesses productivity losses caused by absence, reduced efficiency at work and difficulties in job performance. When patients are absent for less than 1 month this is defined as short-term absence, otherwise it is defined as long-term absence. The SF-HLQ allows calculating the productivity costs according to the Friction Cost Method. The latter method takes into account the economic circumstances that limit the losses of productivity to society as a formerly unemployed person may replace the person who is disabled [14]. Productivity losses are valuated using the average value added per worker by age and gender per day and per hour.

The costs used in economic evaluations for mental health care interventions can be divided in three different types of costs, see Table 1.1[15].

Table 1.1| Types of costs

Types of costs	Examples of costs that fall within this category
Costs in health care sector	Medical costs for prevention, diagnosis, therapy, revalidation and care
Costs of family and patients	Costs of caregivers, patient costs (time/travel costs)
Costs in other sectors	Productivity costs, legal costs, costs for special education

According to the Dutch guidelines for economic evaluations, a societal perspective should be taken[15]. This implicates that an economic evaluation should include the impact of an intervention on the welfare of the whole of society, not just on the individuals or organizations directly involved [16]. Sectors other than the health service may incur costs or benefits as a result of healthcare interventions. To illustrate, Dutch employees with a major depressive disorder work 30 days per year less than their colleagues without the disorder and therefore generate high productivity costs [17]. In general, studies have shown that production losses are responsible for 60-70% of the total costs in patients with mental disorders[18]. Although the inclusion of these costs may have a large impact on the outcomes, most studies conduct an assessment of a more limited perspective and do not include costs outside the health care sector. This is illustrated by the fact that only less than 10% of economic evaluations include productivity costs [19]. Opposite to the costs in the health care sector, which deal with specific activities to treatment or prevention of the disease, the costs in other sectors depend on the population or intervention that is evaluated. For example, although productivity costs may be extremely relevant when the intervention under study is provided to the working population, when adolescents are considered, these costs may become negligible compared to the costs associated with delinquency or absenteeism from school. Costs and quality of life are subsequently used to calculate the ICER. The cost-utility ratio may be compared to different thresholds and the probability of the ICER being acceptable to society may be calculated.

Although economic evaluations are increasingly recognized to be relevant, the number of studies in mental health care is still low; especially those for the non-

pharmaceutical interventions [20] . This is not surprising as regulatory structures focus on drugs and subsequently there is lack of funding for other interventions [20]. However, economic evaluations should also focus on psychological interventions as there is evidence that at least for some disorders psychological treatment (combined with drug treatment) may be more effective [21] and is preferred by most patients [22].

1.3 INNOVATIVE INTERVENTIONS AND COLLABORATION

An innovative treatment that is potentially cost-effective is the collaborative care model. The collaborative model includes a broad range of intervention, settings and providers and its defining characteristics are a team of healthcare professionals responsible for providing the 'right' care at the 'right' time. A care manager is introduced and a collaboration network between the care manager, general practitioner (GP) and consultant psychiatrist is formed [23]. It was initially provided in the USA primary care setting for patients with depressive disorders. Several variations of collaborative care models exist. In the Netherlands, collaborative care was further developed from the Improving Mood: Providing Access to Collaborative Treatment (IMPACT) model from Seattle [24-26], for treatment of depression in the family practice setting, the occupational health setting and the general hospital setting. The model was adapted to support its applicability in the Dutch primary care setting [27]. In the collaborative care model the health care provider works together with other health care professionals [23] to establish a jointly and systematically treatment plan according to a web-based decision aid. The treatment is delivered by the GP, the care manager and/or the consultant psychiatrist (two out of three) [23]. The care manager usually is a non-physician professional, such as a primary care psychologist, a social worker or a psychiatric nurse. In the Netherlands mental health care is organized according to the principle of stepped care. Applying a stepped care approach means that the intensity of the treatment increases when the patient does not recover [28]. Research showed that collaborative care is an effective intervention in patients with a Major Depressive Disorder (MDD) and anxiety disorder [25,26,28,29] in primary care and there are reasons to assume that it might be cost-effective [30-32].
Another group of innovative treatments based on the concept of collaboration are family based interventions. A fundamental assumption of these family therapy approaches is that family engagement and collaboration are essential for

therapeutic progress[33]. These interventions are not only aimed at the individual, but also at systems surrounding the individual such as family and peers. In this way, the therapy not only positively affects the individual but also the family (family cohesion) and the extra-familial systems, as the individual, familial and extra-familial systems are interconnected [34]. Well-known forms of family/family-based treatments are Multisystemic therapy (MST)[35], Functional Family Therapy (FFT)[36] and Multidimensional Family therapy (MDFT) [33]. Family therapy is considered an evidence-based practice treatment for children and adolescents with externalizing disorders, symptoms of delinquency and/or substance use disorder [37,38].

1.4 AIM AND RESEARCH OBJECTIVES

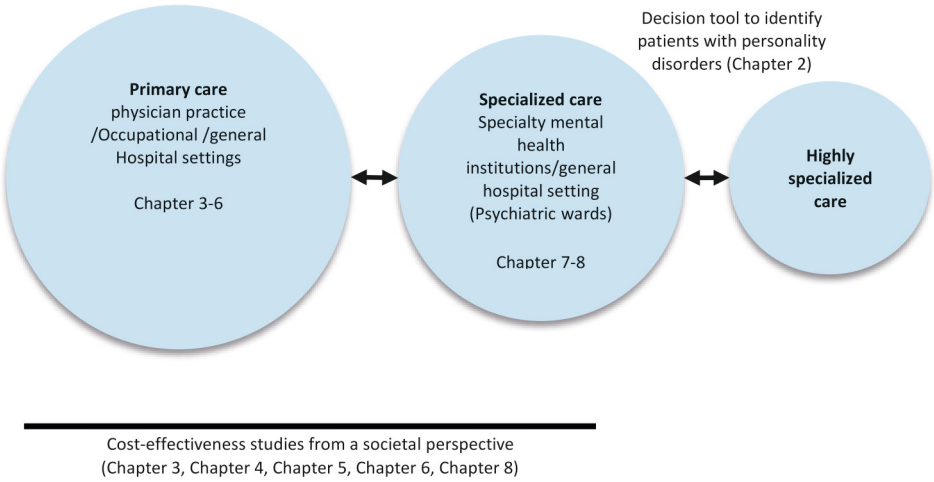
The overall aim of this thesis is to investigate the cost-utility of collaboration models from a societal perspective.
The first part of this thesis concerns the allocation of patients and the development of an evidence based decision tool. In the second and third part of this thesis cost-utility is determined for interventions that have their emphasis on collaboration. The second part contains interventions that have integrated collaboration between settings. More specifically, in these chapters the cost-utility is determined for collaborative care models provided in different settings for two common mental disorders; MDD-and generalized anxiety disorder (GAD) /panic disorders (PD). The third part of this thesis reflects upon interventions that are based on collaboration. In this part, an overview is provided of economic evaluations for family interventions. Additionally, a cost-utility study is conducted for a specific family intervention (Multidimensional Family Therapy (MDFT)), which is provided to adolescents with a substance use disorder, externalizing disorder or delinquency. In Fig. 1.1, a flow diagram shows the main topics of this thesis and how they are connected.

The research questions are as follows:

1. Is it possible to develop a validated tool to identify patients in need of specialized and highly specialized care?
2. Are collaborative care models for two common mental disorders, namely depression and panic/generalized anxiety disorders, cost-effective?

3. Are family interventions in adolescents with mental disorders cost-effective?

Fig 1.1 Flow diagram along the chapters of this thesis



1.5 OUTLINE OF THIS THESIS

Chapter 2 (Part 1, page 11) aims to answer the first research question by developing a decision tool that can guide clinical decision making to refer patients with personality disorders to specialized or highly specialized care. This instrument is developed in collaboration with professionals and researchers. When professionals use the decision tool and refer patients to the most appropriate setting of care, patients may be treated more cost-effective.
Chapter 3, 4 ,5 and 6 (Part 2, page 49) of this thesis focuses on the second research question of this thesis by investigating the cost-utility of two common mental disorders; GAD/PD and MDD. In these studies, the collaborative care models are compared with care as usual and a societal perspective was taken. In Chapter 3, 4 and 5 collaborative care for MDD is examined by using data of three randomized trials using data from the depression initiative. The difference between the chapters is the setting in which the patients are treated. In Chapter 3 patients are treated in an occupational setting, in Chapter 4 they are treated in the family practice setting and in Chapter 5 patients with a comorbid MDD that are chronically ill are treated in the general hospital setting. In Chapter 6 the cost-

utility of collaborative care for patients with a GAD and PD in the family practice setting has been studied. For now, research has only focused on the collaborative care model in the family practice setting for depression in the United States.
Chapter 7 and 8 (Part 3, page 121) address the 3rd research question. Chapter 7 examines scientific evidence on cost-effectiveness studies for family therapy of externalizing disorders, substance use disorders and delinquency by conducting a systematic review. These family therapies are evidence based treatments for these disorders; however, evidence on the cost-effectiveness is limited. Chapter 7 indicated, there was only limited evidence for the cost-effectiveness of MDFT. Therefore in Chapter 8 the cost-utility of MDFT for adolescents with externalizing disorders, substance use disorders and delinquency is investigated by comparing MDFT with Cognitive Behavioral Therapy (CBT). In order to perform the study from a societal perspective, unit costs of delinquency in adolescents were also estimated. By considering interventions targeting common mental health disorders in adolescents, the surplus value of collaboration in treatment can be evaluate

PART 1: ALLOCATION OF PATIENTS

2 DEVELOPING A DECISION TOOL TO IDENTIFY PATIENTS WITH PERSONALITY DISORDERS IN NEED OF HIGHLY SPECIALIZED CARE

Based on: Goorden, M., Willemsen, E.M.C., Bouwmans, C.A.M., Busschbach, J.J.V., Noom, M.J., van der Feltz-Cornelis, C.M., Uyl-de Groot, C.A., Hakkaart-van Roijen, L. (2017). Developing a decision tool to identify patients with personality disorders in need of highly specialized care. BMC Psychiatry, 17: 317

Abstract

Background: Current guidelines recommend referral to highly specialized care for patients with severe personality disorders. However, criteria for allocation to highly specialized care are not clearly defined. The aim of the present study was to develop a decision tool that can support clinicians to identify patients with a personality disorder in need of highly specialized care.

Methods: Steps taken to develop a decision tool were a literature search, concept mapping, a meeting with experts and a validation study.

Results: The concept mapping method resulted in six criteria for the decision tool. The model used in concept mapping provided a good fit (stress value = 0.30) and reasonable reliability (ρ = 0.49). The bridging values were low, indicating homogeneity. The decision tool was subsequently validated by enrolling 368 patients from seven centers. A multilevel model with a Receiver Operating Characteristic Curve (ROC) was applied. In this way, an easily implementable decision tool with relatively high sensitivity (0.74) and specificity (0.69) was developed.

Conclusions: A decision tool to identify patients with personality disorders for highly specialized care was developed using advanced methods to combine the input of experts with currently available scientific knowledge. The tool appeared to be able to accurately identify this group of patients. Clinicians can use this decision tool to identify patients who are in need of highly specialized treatment.

2.1 INTRODUCTION

The prevalence of personality disorders is high. Several studies have suggested that approximately 1 out of every 10 people in the general population has a personality disorder [39]. When compared to disorders like depression or generalized anxiety disorder, the economic burden is large - this is especially true for the economic costs of borderline and obsessive-compulsive personality disorders[40]. Patients with personality disorders are substantial users of primary care and mental health services [40-44], in particular those with borderline personality disorder. When compared to patients with depression or other personality disorders, they receive the highest amount of care [42]. As a subgroup within this group, patients with severe personality disorders often face additional problems with regards to violence, antisocial behaviour and interpersonal relationships and a greater recurrence of self-harm and a greater duration of administered care [45,46]. The quality of life of patients who experience severe and complex personality problems in combination with a personality disorder is comparable to adults with depression [47,48]. As people with personality disorders form a very heterogenous group, the personality disorder diagnosis alone is seldom sufficient for treatment planning [47]. Guidelines advise highly specialized care for patients with more severe personality disorders [49]. This is supported by evidence that indicates that patients with personality disorders are less responsive to usual treatment [47]. However, research concerning the early identification of patients in need of highly specialized treatment is scarce. Therefore in clinical practice, referral to highly specialized care is often only considered after multiple ineffective regular treatments [49]. Thus, patients may receive insufficient and inappropriate treatment [47] and are expected to generate high costs over time.

Referral to highly specialized care may be optimized by improving diagnostics. To date, validated tools for decision support are scarce in psychiatric practice. This is in contrast to other parts of health care, such as oncology or cardiovascular disease. In the absence of validated tools for the identification of patients who may benefit from highly specialized care, clinicians currently rely on overall clinical impressions or severity of symptoms [6].

To develop a validated tool, it is important to first define the characteristics of patients with severe personality disorders. Until now, only a few studies provided

definitions of patients with severe personality disorders. Crawford et al. (2011) [50] showed that only a few of these studies provide such definitions. These definitions fit five main themes: 1) some categories of personality disorders are more severe than others; 2) severity depends on the number of features of a personality disorder; 3) severity depends on the number of categories of personality disorders; 4) severity depends on the level of impairment in social functioning, and 5) severity depends on the risk of harm towards others [14]. Tyrer [45] developed a severity scale for personality disorders based on the number of clusters, the number of personality disorders, the level of impairment in social functioning and the risk of harm towards each other. However, their scale is not based upon a systematic approach to the evidence. Moreover the relationship between severity, as defined by the criteria of the scale, and treatment allocation to highly specialized treatments is unclear. Although the criteria on this already existing severity scale are expected to partly overlap with the criteria for the identification of patients who may benefit from highly specialized care, these criteria may not cover these patients sufficiently.

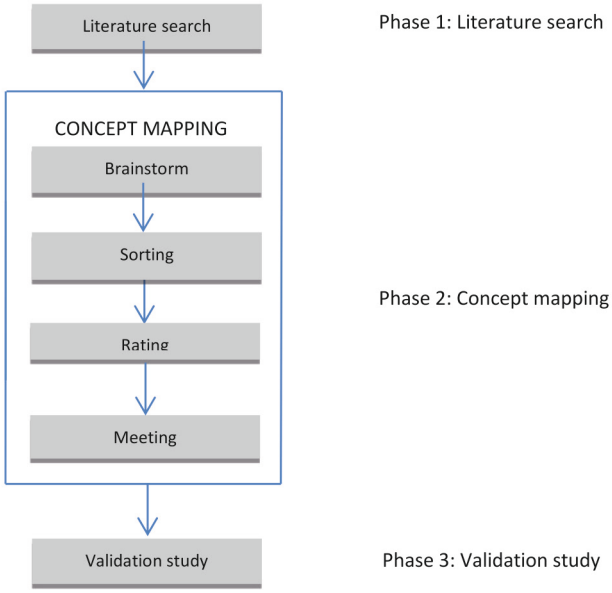
As there is no knowledge on how to identify these patients, the aim of the present study was to develop a decision tool that can aid clinicians in identifying patients with personality disorders in need of highly specialized care.

2.2 METHODS

Study design

The Decision Tool Personality Disorder (DTPD) was developed by clinicians in collaboration with researchers. Its development progressed through three primary phases. During the first phase, a systematic review of the literature was conducted to serve as a scientific foundation for the decision tool. In this phase, experts were asked to suggest search terms in addition to the search terms that the researchers had already generated. In this way, a large set of potential predictors relevant for treatment allocation was formed. In the second phase, a structured conceptualization methodology known as concept mapping was employed to complement the initial list of features. These criteria were provided by clinical experts and used to develop a consensus-based conceptual framework to guide tool development. Experts were asked to sort the potential predictors into distinguishable categories. In this way, a list of items based on the concept mapping results was generated. These items were used to create the DTPD. Experts were consulted at every step to ensure clinical usability. In the third phase, the instrument was studied for its psychometric properties. An overview of the three phases is presented in Fig. 2.1.

Fig 2.1| Flow chart methods



To effectively take key decisions in the concept mapping process, guidelines recommend to use a small group of participants and/or researchers[51]. Therefore, before the study started a small working group was formed. This group consisted of researchers and clinicians from two mental health care institutions (De Viersprong, a mental health centre specialized in personality pathology; PsyQ, a mental health centre for general psychopathology) and a university (Erasmus University, Institute for Medical Technology Assessment), all specialized in the treatment of personality disorders. This working group contacted experienced clinicians who were then invited to complete a digital survey to provide their contact details and the contact details of other experts for participation in the research.

Phase 1: literature search

To develop the first set of criteria for the DTPD, a systematic literature search was conducted in PubMed and Psychinfo. In the absence of studies directly examining factors associated with a need for highly specialized care, proxy indicators had to be identified. The following proxy indicators were defined by experts using a web-based survey: comorbidity, severity, dropout, prognosis and patient characteristics. Search terms were then based on these terms. Studies were first screened by title for selection. Selection was based on eligibility criteria, numbered: (1a) English/Dutch/Human/Abstract or full text available, (1b) Randomized trial/(systematic) Review/Clinical trial/Observational study and (2) published after 1992, (3a) Personality disorder, (3b) Proxy indicators in combination with patient characteristics/comorbidity, and (4) no overlap between studies. For criteria 3b we searched for possible characteristics of patients or certain psychological comorbidities that were associated with having such a proxy indicator - such as certain characteristics that are associated with dropout. Two researchers independently performed the selection process and data extraction of the studies (MG and DS) 1. Differences in selection were resolved by discussion. Following this, the studies were screened for information on predictors/criteria associated with dropout, severity of the personality disorder, predictors for the course of treatment and other prognostic factors. In the review, we have adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

---

[1] M.G (First Author) and D.S. (acknowledgements)

(PRISMA) statement [52]. The criteria defined in the literature search were subsequently used in the concept mapping phase.

Phase 2: Concept mapping

Concept mapping is a method that integrates qualitative research design with quantitative analytic techniques to conceptualize a phenomenon. The concept mapping in the present study consisted of three successive actions for the participants: a brainstorming session, sorting criteria and rating the relevance of criteria. Participants were given access to an online concept mapping system[53]. The web-based concept mapping procedure consisted of three successive steps:

- The brainstorming session: initial criteria from the review were presented to the panel and subsequently the experts were asked to formulate additional criteria which they thought could distinguish between patients who are in need of highly specialized care and patients who are not in need of highly specialized care. The criteria from the literature review and the additional criteria provided by the experts were merged together and subsequently edited for redundancies. Criteria were solely selected by the working group if they related to the focus question and demonstrated a similar abstraction level. Moreover, all criteria had to be clearly defined and overlapping criteria were taken together.
- Sorting the criteria: the experts were asked to sort these criteria into piles on the basis of shared content or theme.
- Rating the relevance of the criteria: experts were asked to rate the perceived importance of the generated criteria on a 6-point scale (1= not important, 6 = very important).

The concept mapping phase resulted in a number of clusters (criteria that were sorted onto the same pile most frequently by clinicians).

A meeting with experts was organized to operationalize the clusters. The overall content of the clusters could not be changed. During the meeting, the participants were given four tasks concerning each of the clusters.

- Examine the variables in the cluster. Which variables do you think should be discarded, or are there other variables that should be included?

- Each cluster should have a name that adequately describes the contents. Can you indicate an appropriate name for this cluster?
- To operationalize the cluster, it is necessary to ask the patient questions. What questions can be asked? Or what questionnaire(s) could be administered to assess how a patient scores on the cluster in question?
- What value should the cluster have for referral to a specific therapy?

On the basis of this process, criteria were added or omitted to the clusters. This meeting was followed by a conference call in which the clusters were operationalized and a first concept decision tool consisting of the clusters (the criteria on the tool) was presented.

Phase 3: Validation study

The concept decision tool was filled out during the intake phase by the clinician and was composed of the criteria that were acquired from the concept mapping phase. One extra question was added to indicate whether the patient needed highly specialized care or not (yes/no). The clinicians based their answer to this question upon clinical impression. During the validation phase, the cut-off point of the final set of criteria was not shown to the therapists. At the end of the validation procedure, a meeting with the expert group was held to determine whether criteria that were not significantly associated with the clinical decision should be included in the final decision tool. A second meeting was organized to determine the cut-off score of the instrument.

Participants

In total, 87 experts were approached to participate in the literature search and the concept mapping phase. 23 of them provided search terms, 28 experts participated in the brainstorming session, 22 in the sorting task and 22 in the rating task. For concept mapping, our goal was to include a minimum of 15 experts to participate, since the average number of participants needed for reliable concept mapping is between 10 and 20 [54]. The data of five of the sorters could not be used due to incorrect execution of the sorting task. The pilot study included 20 therapists evaluating 44 patients, assessing the concept DTPD at the two mental health care institutions. Next, a larger validation study was performed in which seven centres participated, including 88 therapists evaluating 368 patients.

Statistical analysis

Concept mapping software (Concept mapping, 2003) was used for the digital data collection process. Demographic data on the experts regarding sex, age, number of years of experience, title and setting, and the results of the statistical analysis were also collected. SPSS (IBM SPSS statistics, version 19.0.0) was used for the statistical analysis during concept mapping and Excel (Excel, 2010) for building a database during the validation study. R was used for modelling after the validation study. Statistical analysis during concept mapping took the form of an analysis where criteria were grouped into clusters by putting the criteria into clusters that are more similar to one another and by determining the importance of the clusters (by ratings). These clusters were then operationalized and used as the final set of criteria in the validation phase. Statistical analysis in this phase consisted of modelling the final set of criteria and determining a threshold for the set of criteria.

In the concept mapping phase, the frequency by which participants put criteria on the same pile was assessed (see Appendix 2.1 for more details about the analysis). These criteria were then plotted in a two dimensional plane. Criteria that were more similar (based on the frequency by which participants put the same criteria on the same pile) were closer to each other. A “goodness of fit” test that calculated the stress index (a goodness of fit measure) was conducted. Using cluster analysis, the criteria that were more similar to each other were grouped. The working group decided on the maximum and minimum number of groups (clusters). Subsequently, a stepped procedure was followed: starting at the maximum number of clusters, at each step two clusters were combined into one (hierarchical cluster analysis) until a minimum limit was reached. The working group based their decision not only on their clinical expertise (do certain criteria belong together in a cluster?) but also on the average number of clusters the participants had created, and on the bridging values. The bridging values are a measure of coherence between the criteria in the clusters (low means high coherence) and are an indication of the probability of experts sorting those criteria together into a single cluster. The mean value of rating on the 1-6 scale was calculated for each cluster and tested on significant differences to assess if the clusters should be weighed evenly. Reliability was subsequently evaluated by means of the point-biserial correlation, through which the correlation between individual sorting and group sorting was determined. The clusters acquired from concept mapping were considered to be the criteria on the decision tool.

For the validation study of this decision tool, similarity of the criteria with clinical decision was examined in a pilot study by calculating the percentage where a specific criterion was checked as positive and where at the same time clinicians indicated that this patient should be referred to highly specialized care. In the validation study, criterion validity was assessed. For criterion validity, the sensitivity and the specificity of the decision tool were evaluated. Sensitivity is the ability of the instrument to identify patients that belong to highly specialized care. Specificity is the ability to identify those patients that do not belong to highly specialized care. To determine whether patients do (or do not) belong to highly specialized care, clinical judgement was used. A multilevel model was applied as we expected that the clinical decisions within each treatment centre would correlate more than the clinical decisions between the centres. A binomial family of functions was used with a logit link function. The correlation structure was "exchangeable". Using this model, sensitivity and 1-specificity were plotted in a Receiver Operating Characteristic Curve (ROC curve). Subsequently, the Area Under the Curve (AUC) was calculated. When sensitivity and specificity are both high, the AUC approaches 1. By using this model we could determine which of the criteria correlated significantly with clinical decision. Subsequently, easily implementable scoring systems were tested; the criteria were summed and sensitivity and specificity were determined at the specific cut-off points. For internal consistency, we calculated Cronbach's Alpha.

2.3 RESULTS

Phase 1: Literature search results

Respectively 8,912 and 5,025 studies were retrieved in PsycINFO and PubMed. These studies were selected according to the selection criteria (Fig. 2.2). The review yielded 11 studies, including four reviews and seven observational studies. Most of the studies considered patients with borderline personality disorders (BPD). Criteria found in the studies were mostly positively related to a specific treatment outcome or dropout, see Table 2.1 After removal of the duplicates, this resulted in 71 criteria, see Appendix 2.2. As none of these criteria were known to be directly related to referral of patients to highly specialized care, they were used in the brainstorm phase as input for the experts in formulating criteria for referral.

Fig 2.2| Literature search: Flow diagram and studies selected for literature search

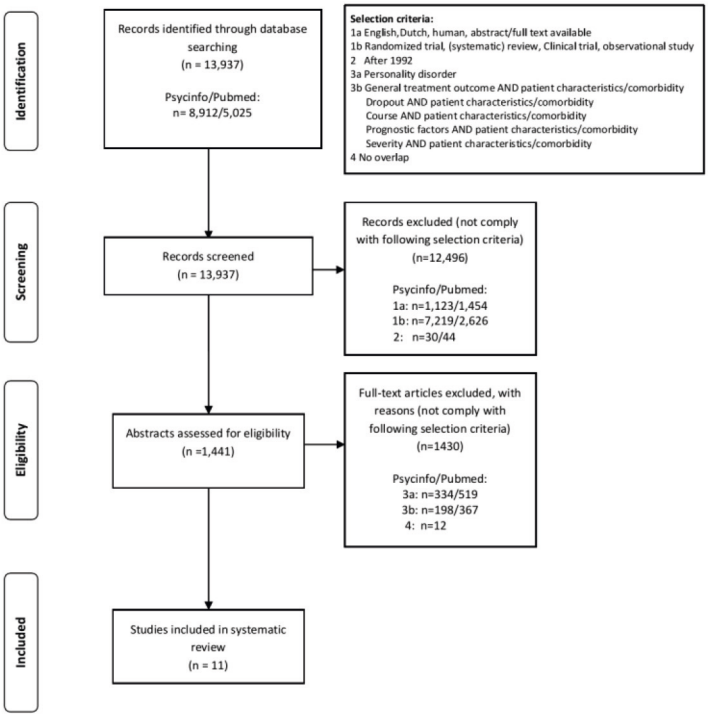


Table 2.1| Results of the literature review

Author	Type PS	Type of article	Criteria	Positive effect on
Barnicot, K. et al. (2011) [55]	BPD	Systematic review	Schizoid personality disorder High level of impulsivity Less pre-treatment suicidal behavior Lack of motivation to change Less internal, more external motivation to change Experiencing higher stigmatization Experiential avoidance Higher trait anxiety Higher anger level	Dropout
Barnow, S. et al. (2010) [56]	BPD	Review	Substance use disorders	Treatment outcome (suicidality/remission time)
Chiesa, M. et al. (2011) [57]	PD	Observational study	Deliberate self-harm	DSM-IV-(comorbidity)
Goodman, G. et al. (1998) [58]	BPD	Observational study	Initial depression and initial psychotic symptoms	Treatment outcome (SCID-P-comorbidity/ SCL-90R-symptom checklist)
Gunderson, J. G. et al. (2006) [59] [59,60]	BPD	Observational study	Meet several criteria for obsessive-compulsive personality disorder Number of borderline personality disorder criteria Number of personality disorder criteria Number of axis-I disorders Early history of abuse and neglect Low GAF score Lower quality relationships	Treatment outcome (DSM-IV-Number of criteria/ lower GAF score)
McMurran, M. et al. (2010) [61]	PD	Systematic review	Lower age Lower level of educational attainment Lower-skilled occupation level Unemployed Convicted in court as an adolescent	Dropout

Author	Type PS	Type of article	Criteria	Positive effect on
			Parental divorce before the age of 10 Emotional neglect during childhood Less time alone Being in a relationship for less than six months Meet more than one PD diagnoses Meet more PD criteria Diagnosis of obsessive-compulsive PD, severe histrionic or antisocial PD and no specific PD Having a dependent PD Have a personality disorder in cluster A or B Higher level of narcism Higher level of impulsivity Fewer suicide attempts Higher trait anxiety Still be in the pre-consideration stage of change Less persistence Higher levels of avoidance Poor rational social problem-solving ability High level of carelessness in problem-solving High level of impulsivity in problem-solving More social competence Poor ego structure Less primitive defence Weaker adaptive defence style A greater denial of need for closeness Have conflicts regarding engagement and abandonment Fear of impulsive breakthrough of negative affect More externalizing defence Projective identification Lower level of general functioning Previous substance abuse Depressive self-image Less depressed	

Author	Type PS	Type of article	Criteria	Positive effect on
			No mood disorders Problems are focussed in one area	
Ryle, A. et al. (2000) [62]	BPD	Observational study	History of self-cutting Unemployed Alcohol abuse	Dropout
Skodol, A. E. et al. (2002) [63]	BPD	Review	Childhood sexual abuse Incest Lower age at first psychiatric contact Symptom chronicity Affective instability Magical thinking Aggression in relationships Impulsivity Substance abuse More Schizotypical features More Antisocial features More Paranoid features Number of borderline personality disorder criteria A greater number of axis II disorders Comorbidity of axis I and II disorders	Treatment outcome (DSM-IV: diagnostic criteria of borderline)
Thormählen B. et al. (2003) [64]	PD	Observational Study	Have a personality disorder in cluster A or B More distress Focus on 1 specific interpersonal problem Lower Age	Dropout
Yen, S. et. Al (2002) [65]	BPD, Schizotypical, Avoidant, and Obsessive Compulsive PD	Observational study	Measured number of physical attacks on another person in the past (with and without a weapon) More exposure to various types of trauma More lifelong PTSD Lower age at first traumatic experience	Severity (DSM-IV: more severe: Schizotypal, BPD; other types)
Yoshida, K. et al. (2006) [66]	BPD	Observational study	Overinvolvement in family relationships	Treatment outcome (lower GAF score)

Phase 2: Concept mapping results

27 experts completed questions about their demographics, see Table 2.2 The average age of the participants was 49 years, with on average 20 years of working experience. Most experts were psychiatrists working in an outpatient mental health care setting.

Table 2.2| Demographic variables

Demographic variables; concept mapping (N=27)	
Sex (N(%) male)	15 (55%)
Mean age	48.85 (SD=7.88)
Mean years of professional experience	20.37 (SD=9.37)
Occupational setting (N(%))	
Nursing department	6 (22%)
Daycare	5 (19%)
Ambulatory mental health care institute	15 (56%)
Ambulatory private practice	1 (4%)
Discipline(N (%))	
Psychiatrist	18 (67%)
Psychotherapist/Clinical psychologist	6 (22%)
GZ psychologist	1 (4%)
Researcher	2 (7%)

Results of the brainstorm process

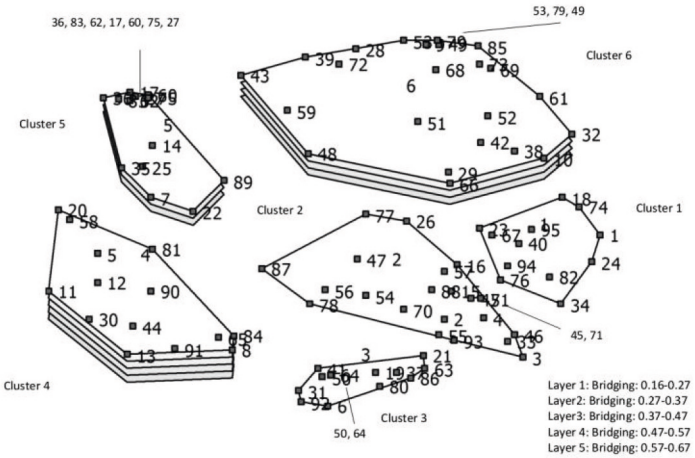
Following the brainstorming session, another 35 criteria were added to the criteria of the literature search. Selection of the criteria left a remaining total of 95 criteria, see Appendix 2.2. These criteria were included in the concept mapping system.

Results of the sorting process

The average number of clusters created by the participants during the sorting process was 10 (Range 5-23). The working group decided on a maximum number of clusters of 15 and a minimum of two with an optimal number of clusters of 6. In general, the bridging values (level of homogeneity) were low or acceptably low, which indicates a high homogeneity level for these six clusters. Cluster 4 exhibited the highest bridging value. The bridging values and the criteria in the clusters are shown in Appendix 2.3.

The clusters were presented in a cluster map with bridging values, see Fig. 2.3. This revealed that there were three clusters with very low bridging values (Cluster 1, Cluster 2, Cluster 3), indicating a high degree of cluster homogeneity. Goodness of fit was tested using the stress value (0 = very stable, 1 = distances between the criteria are completely at random). A stress value of 0.30 was found, which meant that the model fitted the data reasonably well.

Fig 2.3| Cluster map with bridging scores.



Results of the rating process

The rating values per cluster are given in Appendix 2.3. Cluster 6 had a high rating score, despite its high bridging value. This means that, although the clinicians rated the criteria as important, the criteria often were not sorted into the same cluster (i.e. were not homogeneous). A t-test was performed to examine whether the scores from the rating task varied between the different clusters. As multiple t-tests were performed, a Bonferroni correction was applied ($p < 0.003$). Significant differences were found between cluster 1 and cluster 2. Also, a significant difference emerged between cluster 1 and cluster 3. This is caused by the higher rating of cluster 3 and cluster 2 as compared to cluster 1.

Results of the (final) expert meeting

Five experts attended the meeting, and three submitted input for the discussion in advance by email. During this meeting, the various clusters were defined that represented the content. They determined that six clusters that would be used. A relatively large number of variables were moved into cluster 6, which was in line with the high bridging values and corresponding low level of homogeneity in this cluster. Cluster 1, 2, 3, 4 and 6 were respectively operationalized as "Severe negative effect with disadaptive coping", "Severe destructive behaviour to oneself or others", "Multiple comorbid disorders on axis I and/or axis II due to severe psychiatric problems", "Severe chronic traumatisation in childhood", "Severe social and societal dysfunction: Global Assessment of Functioning (GAF)[2]<45" and "Difficulties in developing a therapeutic relationship". "Specialized treatment was not successful" was added. Also "Possibility and willingness to strictly follow minimal treatment conditions" was added as a starting point for assessing patients with the checklist. After the conference call, the set of criteria was finalized. All clusters were evenly weighted based on relevance. As there was not much difference in rating between the clusters, it was decided to weight them evenly. A preliminary cut off point was also chosen during the conference call (score ≥4).

Reliability:

*R*eliability was estimated by correlating each individual sort matrix with the total matrix. The resulting correlations were all averaged. The reliability, if no Spearman-Brown correction was used, was 0.49.

Phase 3: Validation study results

Pilot study:

The similarities of the outcome of the criteria with clinical judgement were as follows: severe negative effect with disadaptive coping (77%), severe destructive behaviour to oneself and others (67%), multiple comorbid disorders on axis I and/or axis II due to severe psychiatric problems (72%), severe social and societal dysfunction: GAF<45 (62%), severe chronic traumatisation in childhood (74%),

---

[2] GAF=Global Assessment of Functioning scale[19]. It is a scale that is used by clinicians for rating social, occupational and psychological functioning of an individual.

difficulties in developing a therapeutic relationship (72%) and specialized treatment was not successful (81%). All criteria were highly similar. Severe social and societal dysfunction had the lowest similarity. Subsequently, we changed the cut-off score to GAF≤50 because this yielded a higher similarity (68%).

Validation study

Demographics:

The characteristics of patients and therapists are shown in Table 2.3. There was no significant difference between the characteristics of the patients in the specialized and highly specialized care group. For therapists, only years of experience differed between the groups. In highly specialized care, therapists had more years of experience when compared to specialized care, see Table 2.3 (t(67.52)= 4.16, p-value = 9,2*10^-5).

Table 2.3| Characteristics patients/therapists divided into specialized/ highly specialized care

		highly specialized care (Patients: N=110; Therapists: N=29)	Specialized care (Patients: N=268; Therapists: N=59)
		Mean (sd)/percentage (%)	Mean (sd)/percentage (%)
Patients			
	Age (years) Gender (% men)	35,0 (11,7) 34% (35)	33,9 (10,6) 28% (64)
Therapists			
	Age (years)	42.4 (11.2)	33,9 (10,4)
	Experience therapist (number of years)	16.3 (8.7)**	8.7 (7,1)**
	Talked to patient during intake (% Yes)	94.9%	100%

*p<0.05, **p<0.01

Model:

A multilevel model was applied. An overview of the outcomes in the model is showed in Table 2.4.

Table 2.4| Multilevel model

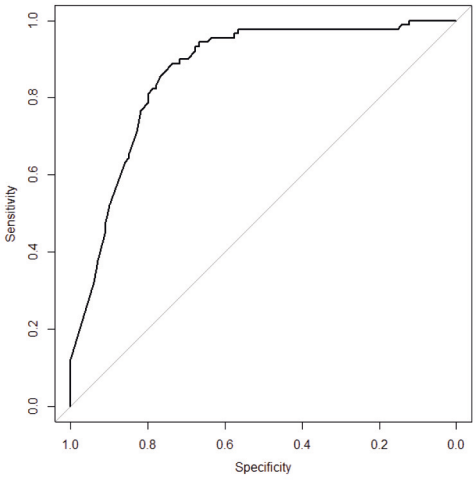
	Estimate	SE	p-value
Severe negative affect with disadaptive coping	2.530693	0.616013	3.99e-05 **
Severe destructive behavior to oneself or others	0.917365	0.234275	9.01e-05*
Multiple comorbid disorders on axis I and/or axis II due to severe psychiatric problems	1.737646	0.849724	0.04086 *
Severe social and societal disfunction: GAF≤50	0.825936	0.380961	0.03016*
Severe chronic traumatisation in childhood	0.214238	0.807725	0.79083
Difficulties in developing a therapeutic relationship	-0.004092	0.265995	0.98773
Treatment in specialized care was not successful	1.208202	0.387603	0.00183 *

*p<0.05, **p<0.01

ROC curve:

A ROC curve was plotted for the model, see Fig. 2.4. The area under the curve was high for the model, 0.865 (95% CI: 0.812-0.918) and subsequently the model discriminated well between low and high risk observations.

Fig 2.4| ROC curve



Cronbachs alpha:
Cronbachs alpha was 0.69.

Meeting:
During the meeting the experts agreed upon the criteria being part of the decision tool, as they cover expert opinion.

Scoring system:
In table 2.5, the criteria were summed and sensitivity and specificity were determined at the specific cut-off points. A cut-off score of 4 and a cut-off score of 5 were associated with relatively good sensitivity and specificity, see Table 2.5.

Table 2.5| Number of criteria positively scored in relationship to sensitivity and specificity

Number of criteria positively scored	Sensitivity	Specificity
1 criteria or more	0.88	0.31
2 criteria or more	0.85	0.41
3 criteria or more	0.83	0.52
4 criteria or more	0.78	0.69
5 criteria or more	0.70	0.85
6 criteria or more	0.50	0.94
7 criteria	0.18	0.98

Meeting:
In the second meeting, the experts agreed that it was more important for the tool to be sensitive rather than specific, and subsequently a cut-off score of 4 was chosen. The decision tool was then finalized, see Table 2.6.

Table 2.6| Decision tool

Centre:		
Department:		
Name of professional/intaker:		
Name of patient:		
BSN number of patient:		
	Yes/No	Value or finding
1. Severe negative affect with disadaptive coping	Yes No	
2. Severe destructive behavior to oneself or others	Yes No	
3. Multiple comorbid disorders on axis I and/or axis II due to severe psychiatric problems	Yes No	
4. Severe social and societal disfunction: GAF≤50	Yes No	
5. Severe chronic traumatisation in childhood	Yes No	
6. Difficulties in developing a therapeutic relationship	Yes No NA*	
7. Treatment in specialized care was not successful	Yes No NA	
Number of times positively scored (=YES) Score ≥4?	Yes -> Go to question 8 No-> Not referred to highly specialized care based on this decision tool	
8. Possibility and motivation to conform to minimal treatment conditions for psychotherapy in intensive (day)care	Yes -> Referred to highly specialized care based on this decision tool No-> Not referred to highly specialized care based on this decision tool NA-> Referred to highly specialized care based on this decision tool	

*NA=Not Applicable

2.4 DISCUSSION

Based on evidence from literature, a consensus method and a validation study a decision tool was developed to identify patients who may benefit from highly specialized care. Experts were consulted at every step to ensure good clinical relevance. The meetings ensured that the experts played a decisive role in the realization of the final result, while at the same time taking into account the generated clusters and ratings derived from the systematic concept mapping approach.

The DTPD consisted of seven criteria, as shown in table 2.6. The criteria "Multiple comorbid disorders on axis I and/or axis II due to severe psychiatric problems", "Severe social and societal dysfunction" and "Severe destructive behaviour to oneself or others" were similar to the criteria of "Comorbidity", "Social functioning" and "Harm towards others" were found in the studies of Tyrer[45] and Crawford, Koldobsky, Mulder, and Tyrer [50]. As in the validation study, these criteria were significantly associated with clinical judgement. However, our decision tool also contained additional criteria that were considered important for clinical judgement, two of which were also significantly associated with clinical judgement. This may indicate that by using a systematic method, we covered a wider range of criteria compared to other studies.

Limitations

Although a decision tool was developed that may cover a wide enough range of criteria to identify patients with personality disorders for highly specialized care, there are some limitations that need to be addressed. One limitation of the review was that an explicit statement containing information on the participants, interventions, comparisons, outcomes, and study design (PICOS) was not included. This approach was chosen to increase clarity, as the objective of this study was very broad (all interventions/comparisons were included and patients who were more severe and less severe were compared). Secondly, bias and quality of the studies was not assessed. All studies and subsequently all criteria on the decision tool that were found were included to minimize the risk of deleting important criteria. However, in the rating phase of concept mapping the importance of the criteria was assessed by the experts and criteria that were not relevant were excluded.

A limitation of the concept mapping methodology is that no specific combinations of criteria can be created in the concept mapping system. For example, when the combination of comorbid disorders and low functioning is considered to be important for referral to highly specialized care but the separate criteria are not, it was not possible to address this issue in the digital system. However, when relevant, combinations were discussed during the final meeting. In future studies, it might be feasible to define these combinations in a more structured manner and at an earlier phase by arranging a separate focus meeting or by using an additional consensus method for defining combinations (such as the Delphi method).
Although the goal of the decision tool is to prevent ineffective treatment for patients with a personality disorder, "Treatment in specialized care was not successful" was a criterion of the tool. The reason behind this is that in reality many patients still have ineffective treatments. Additionally, the criterion was frequently mentioned by clinicians and rated as important. The concept mapping model fitted the data reasonably well (stress value was 0.30). According to Kane & Trochim [51] a value of between 0.20 and 0.35 implies a reasonable fit. This finding is underscored by a meta-analysis of concept mapping studies, in which 95% of the stress values ranged between 0.205 and 0.365[67]. The reliability of our study was reasonably high, compared to the studies of Bedi[68] and Van Manen et al. (2012)[67] which found reliability estimates of respectively 0.45 and 0.56.
A limitation of the pilot and validation study is that clinical judgment was used as a gold standard. However up to date, there are no other validated questionnaires that can be used to measure the same construct. An additional limitation was that only one therapist provided input on both clinical judgment and on the criteria of the decision tool. This may have contributed to bias in the validation study and in future studies this should be addressed. As for the psychometrics, the interrater reliability was not assessed - and thus the degree of agreement between therapists is not known. In addition to this, the construct validity was not measured as we did not have any instrument which would measure the same construct. In future studies the interrater reliability should be assessed and when possible the construct validity. The internal consistency assessed by Cronbach's alpha was relatively low. When criteria all measure one construct, Cronbach's alpha would be high. However, a psychological construct consists of several different related aspects. When the construct is broader, as in the current study, more aspects are measured and the Cronbach's alpha score will automatically be lower. In this way, a low alpha is not necessarily a disadvantage and may not prove a useful estimate.

The selection of items on the instrument during the concept mapping phase ensured that only criteria that were thought to be clinically relevant by the experts were part of the decision tool.
The results from the pilot study showed promise as the correlation between clinical judgement and judgement based on the set of criteria were high. The validation study confirmed the positive results for this study as the decision tool had high sensitivity and moderate specificity.
Although several forms of psychotherapy have proven to be effective in the treatment of personality disorders[69], not all patients profit from these treatments. Studies indicate that patients with more severe and complex personality disorders or specific characteristics may not profit from treatment [24] and are more prone to dropout [20]. Subsequently, they often have a long treatment history with negative results. There is, however, growing attention on early detection and early intervention to confine future damage caused by personality disorders [70]. The decision tool can be used in such a way as it may detect severe patients in an earlier stage of the disorder and improve their prognosis.

Conclusion
In this study, we developed a decision tool to identify patients with personality disorders who may benefit from highly specialized care. This decision tool can be used by clinicians to identify patients who are in need of highly specialized treatment. Future research should focus on replication of this research in order to address the limitations in the current study and subsequently evaluate the long-term costs and quality of life of patients who are referred using the decision tool.

Appendix 2.1 Statistical analysis

A two-dimensional matrix, or 'individual binary symmetric similarity matrix' as this is known, was created for each participant. These individual sort matrices were then added together to obtain a 'combined group similarity matrix'. Next, via non-metric multidimensional scaling (nDMS), all the points from the matrix were mapped, using an iterative approach, in a two-dimensional plot. The stress index is subsequently used as an index for the "goodness of fit" of the model (0=very stable, 1= distances are wholly random).

Clusters were created with the help of 'agglomerative hierarchic cluster analysis', in which use was made of Ward's minimum variance algorithm.[71] First, the number of clusters was decided on, after which, at each stage in the analysis, two clusters were combined into one. Hence, first a decision had to be made about the maximum and minimum number of clusters, and the cut-off point for the number of clusters. Based on the bridging values and the average number of clusters, the working group respectively defined a minimum and a maximum number of clusters was defined, and the cut-off point. The bridging value is a measure of the coherence between the criteria in the clusters (0=high degree of homogeneity, 1 = low value of homogeneity). The clusters and the bridging values were then once again plotted in a two-dimensional map.

Subsequently, the rates of the clusters were examined on significant differences t-tests (with Bonferroni correction). The reliability was subsequently evaluated by means of the point-biseral correlation, through which the correlation between individual sorting and group sorting was determined.

Appendix 2.2 Final set of criteria obtained via literature search or by brainstorming

Criterion	Literature search	Brainstorm additional
A greater denial of the need for intimacy	✓	
More affective instability	✓	
Antisocial PD	✓	
More magical thinking	✓	
Low level educational attainment	✓	
Comorbid Axis I, II and III disorders		✓
Lower age at first psychiatric contact	✓	
Recent medical history shows numerous crisis admissions		✓
NO willingness to change		✓
Have conflicts regarding involvement and loneliness	✓	
He/she costs society too much money		✓
Lower occupation level	✓	
Lower level of general functioning	✓	
A pathogenic home environment	✓	
Poor ego structure	✓	
Weaker adaptive defence style	✓	
Incest	✓	
Higher level of neurosis	✓	
Psychotic symptoms	✓	
Being in a relationship for less than 6 months	✓	
More than one personality disorder	✓	
Less psychotropic medication		✓
No specific PD	✓	
Fear of sudden breakthrough of negative affect	✓	
Lower age at first traumatic experience	✓	
High level of carelessness in solving problems.	✓	
Emotional neglect during childhood	✓	
Investment in therapy is practically feasible		✓
High burden of suffering		✓
Unemployed	✓	
Comorbidity complicated somatic suffering		✓
Low compliance	✓	
Obsessive-compulsive personality disorder criteria	✓	
Fear disposition	✓	
Lower age	✓	

Criterion	Literature search	Brainstorm additional
Complications during pregnancy and childbirth		✓
Schizotypal comorbidity	✓	
Less perseverance	✓	
Inability to enter into a stable therapeutic relationship		✓
Mere externalizing defence	✓	
Comorbid severe form of dissociative disorder		✓
Higher hostility level		✓
Tried in court as an adolescent	✓	
Longstanding pattern of dysfunction		✓
High level of impulsivity	✓	
Diagnosis of obsessive-compulsive PD	✓	
Unclear diagnosis		✓
Experience higher stigmatization	✓	
Low motivation, but some motivation to (be able to) comply with minimal treatment conditions		✓
Axis 1 comorbidity		✓
Aggression		✓
Sufficient capacity for change		✓
Less internal, more external motivation to change	✓	
Crisis susceptibility		✓
Meet a higher number of PD criteria	✓	
Higher level of symptom chronicity	✓	
High level of impulsivity in solving problems	✓	
Less time alone	✓	
Measured number of physical attacks on another person in the past (with and without a weapon)	✓	
Complex trauma in early childhood		✓
Investment in treatment possible as regards ego strength		✓
Separation from parents before age 10	✓	
Schizoid personality disorder	✓	
Comorbid depression	✓	
Higher number of lifetime para suicides		✓
Poor rational social problem-solving ability	✓	
High anger level	✓	
Urgent need for change		✓
Show willingness to change		✓
Suicidal tendencies		✓
Impulsivity	✓	

Criterion	Literature search	Brainstorm additional
Sufficient (minimal) adaptive capacity to function in a group or therapeutic environment		✓
Still be in the pre-consideration stage of change	✓	
More avoidance based on experience	✓	
More exposure to different types of trauma	✓	
Evident problems in level of personality functioning, in personality organization.		✓
More aggression in relationships	✓	
More antisocial comorbidity	✓	
Lack of motivation to change	✓	
Paranoid comorbidity	✓	
A few isolated areas of health		✓
Projective identification	✓	
Childhood sexual abuse	✓	
Low GAF score with downward spiral	✓	
NO willingness to change, but sufficient willingness		✓
Have a personality disorder in cluster A and B	✓	
PTSD	✓	
Deliberate self-harming	✓	
Prior second echelon treatment yielded insufficient result.		✓
History shows more than one involuntary commitment		✓
Unable to move forward in several areas of life (work/school, social network and leisure activities)	✓	
Comorbid addiction	✓	
Severe histrionic PD	✓	
Higher level of narcissism	✓	
More avoidance	✓	

Appendix 2.3 Cluster with average bridging and rating values

Clusters	Average Bridging value (SD)	Average rating value (SD)
Cluster 1	0.25 (0.11)	3.47 (0.47)
Higher level of neurosis More avoidance based on experience Fear of sudden breakthrough of negative affect A greater denial of a need of intimacy Higher level of narcissism Evident problems in level of personality functioning, in personality organization. High anger level No specific PD More externalizing defence Projective identification More avoidance Fear disposition		
Cluster 2	0.16 (0.14)	3.9 (0.41)
Meet a higher number of PD criteria More affective instability Higher level of impulsivity Impulsivity Severe histrionic PD More magical thinking Diagnosis of obsessive-compulsive PD Obsessive-compulsive personality disorder criteria Antisocial PD Deliberate self-harming Suicidal tendencies High level of impulsivity in problem-solving Poor ego structure Weaker adaptive defence style Crisis susceptibility High level of carelessness in problem-solving Unclear diagnosis More aggression in relationships High level of symptom chronicity PTSD More antisocial comorbidity		
Cluster 3	0.19 (0.09)	4.05 (0.48)
Comorbid Axis I, II and III disorders Axis I Comorbidity Comorbid depression Comorbid addiction Comorbid severe form of dissociative disorder Comorbidity complicated somatic suffering More than one personality disorder Paranoid comorbidity Have a personality disorder in cluster A and B Schizoid personality disorder Psychotic symptoms Schizotypal comorbidity		

Clusters	Average Bridging value (SD)	Average rating value (SD)
Cluster 4	0.67 (0.17)	3.74 (0.97)
History shows more than one involuntary commitment Unemployed Lower occupation level Low level of educational attainment He/she costs society too much money A few isolated areas of health Less time alone Being in a relationship for less than 6 months Low GAF score with downward spiral Recent medical history shows numerous crisis admissions Higher number of lifetime para suicides Longstanding pattern of dysfunction Inability to move forward in several areas of life (work/school, social network and leisure activities) Lower level of general functioning		
Cluster 5	0.46 (0.19)	3.73 (0.84)
Lower age at first traumatic experience Previous second echelon treatment yielded insufficient result. Lower age at first psychiatric contact A pathogenic home environment Lower age Less psychotropic medication Childhood sexual abuse Complications during pregnancy and childbirth Parental divorce before the age of 10 Incest Complex trauma in early childhood More exposure to different types of trauma Emotional neglect during childhood		
Cluster 6	0.48 (0.15)	3.83 (0.49)
No willingness to change, but sufficient willingness Show willingness to change Still be in the pre-consideration stage of change Low motivation, but some motivation to (be able to) comply with minimal treatment conditions No willingness to change Lack of motivation to change Less internal, more external motivation to change Urgent need for change Experience higher stigmatization Measured number of physical attacks on another person in the past (with and without a weapon) Sufficient (minimal) adaptive capacity to function in a group or therapeutic environment Investment in therapy is practically feasible Tried in court as an adolescent Inability to enter into a stable therapeutic relationship Poor rational social problem-solving ability High burden of suffering		

Clusters	Average Bridging value (SD)	Average rating value (SD)
Less perseverance		
Higher hostility level		
Aggression		
Has conflicts regarding involvement and loneliness		
Investment in treatment possible as regards ego strength		
Sufficient capacity for change		
Low compliance		

PART 2: COLLABORATION BETWEEN SETTINGS

3 COST UTILITY ANALYSIS OF A COLLABORATIVE CARE INTERVENTION FOR MAJOR DEPRESSIVE DISORDER IN AN OCCUPATIONAL HEALTHCARE SETTING

Based on: Goorden M., Vlasveld M.C., Anema J.R., van Mechelen W., Beekman A.T.F., Hoedeman R., van der Feltz-Cornelis C.M., Hakkaart-van Roijen L. (2014). Cost utility analysis of a collaborative care intervention for major depressive disorder in an occupational healthcare setting. Journal of Occupational Rehabilitation, 24(3): 555-562

Abstract

Background: Major depression is associated with high levels of absence and reduced productivity. Therefore the costs to society are high. The aim of this study was to evaluate the cost-utility of collaborative care for major depressive disorder (MDD) compared to care as usual in an occupational healthcare setting. A societal perspective was taken.

Methods: In this randomised controlled trial, 126 sick-listed workers with MDD were included (65 collaborative care, 61 care as usual). Baseline measurements and follow up measures (3, 6, 9 and 12 months) were assessed by questionnaire. We applied the Trimbos/iMTA questionnaire for costs associated with psychiatric illness, the SF-HQL and the EQ-5D respectively measuring the health care utilization, production losses and general health related quality of life.

Results: The average annual healthcare costs in the collaborative care group were €3,874 (95% CI €2,778– €5,718) compared to €4,583 (95% CI €3,108–€6,794) in the care as usual group. The average quality of life years (QALY's) gained were lower in the collaborative care group, 0.05 QALY. The majority of the ICERS (69%) indicate that collaborative care is less costly but also less effective than care as usual. Including the productivity costs did not change this result.

Conclusions: The cost-utility analysis showed that collaborative care generated reduced costs and a reduction in effects compared to care as usual and was therefore not a cost-effective intervention.

3.1 INTRODUCTION

Among the Dutch working population, major depressive disorder (MDD) is one of the most prevalent mental disorders, occurring in more than 4% of this population [17]. Because of the high rate of sick leave (absenteeism) and reduced efficiency at work (presenteeism) the associated burden of MDD is high for the patient as well as for society. A recent study showed that due to productivity loss, encompassing absenteeism and presenteeism at work, Dutch employees with MDD work 30 days per year less than their colleagues without this disorder [17].

The importance of productivity loss due to depression was already emphasized in several studies. The incidence of depression is the highest in middle aged individuals (25–45) [72], which may indicate that depression strongly affects society's productivity, especially in light of the recurrent nature of the disease. Productivity costs are known to be a large part of the total costs of depression [5,18]. In the case of depressive disorder, the productivity costs, amount to €242 million per million workers [17] and on average account for 60–70% of the total costs [5,18]. Therefore, effective interventions that may reduce productivity loss due to depression are potentially cost-effective. Although evidence-based treatments for MDD are available, these treatments are not always implemented correctly and experience obstacles, especially in the occupational healthcare setting. Dutch employees on sickness absence due to mental health problems have access to an occupational physician (OP) and general practitioner (GP). However, as a consequence of the separation of treatment and sickness certification in the Dutch social legislation, there is a lack of communication and agreement between them [73]. In addition, there are long waiting lists for specialized treatments of sick-listed employees with mental health problems. Finally, there is lack of monitoring of treatment, and effective treatment methods are insufficiently applied [73]. The collaborative care model is introduced to address these problems, by actively monitoring employees and increasing the collaboration between healthcare professionals. Research showed that the collaborative care model is an effective intervention, on short- and long-term outcomes in MDD [74]. According to a recent systematic review, there is evidence that collaborative care may also be a cost-effective approach for MDD [32]. However, until now research has only focused on the collaborative care model in the primary care setting and not in the occupational healthcare setting. A recent study among workers with common mental disorders showed that linking the

expertise of OPs with that of a consultant psychiatrist resulted in a faster return to work [75]. The findings of Vlasveld et al. [29] indicated that although collaborative care with an integrated work place intervention in the occupational healthcare setting reduced the time until response, it did not have a significant effect in terms of time to remission, duration to return to work and the intensity of depressive symptoms in the occupational healthcare setting. Consequently, the reduced time until response in the collaborative care group is not the only element that affected return to work. It is possible that although the increased response in the collaborative care group did not influence return to work, it may have a positive influence on quality of life, measured in Quality of Life Years (QALY's) gained, an outcome measure often used in economic evaluations. Because the duration until return to work did not differ significantly between both groups, a difference in productivity costs between them might not be expected. However, collaborative care may work in a more efficient way in terms of resource use, because of the low intensity in the first steps of treatment and therefore may lead to lower healthcare costs compared to care as usual [76]. Therefore, the aim of this study was to evaluate the cost-utility of a collaborative care intervention in sick-listed employees with MDD. A cost-utility analysis is a specific form of a cost-effectiveness analysis. The advantage of this analysis is that the intervention is not only comparable to interventions in the mental health care system, but also to interventions outside the mental health care system. The analysis was conducted from a societal perspective, meaning that all relevant costs and effects were taking into account. The intervention was applied by an OP acting as care manager and was compared to care as usual.

3.2 METHODS

Randomization and Recruitment

The cost-utility analysis was conducted along a randomized controlled trial (RCT), evaluating the effectiveness of collaborative care versus care as usual in the Dutch occupational healthcare setting. Results of this RCT on the effectiveness of collaborative care have been described elsewhere [29,76,77]. Computer-generated randomisation took place at employees' level. In both groups, employees received sickness guidance as usual by their company's OP. In addition, employees in the intervention group received collaborative care treatment from an OP-care manager, who was guided by a web-based stepped care protocol and a consultant psychiatrist. OP-care managers were recruited at the occupational health service. They received training prior to the start of the study and close supervision during the study to fulfil the role as care manager. Employees in both groups were free to engage in any other treatment as well. Employees sick-listed between 4 and 12 weeks due to mental disorders were screened for depressive symptoms with the 9-item depression subscale of the Patient Health Questionnaire, the PHQ9 [78]. If they scored screen positive, the mini-International Neuropsychiatric interview (MINI PLUS International Neuropsychiatric interview) was administered [79]. At inclusion, employees were immediately sent the baseline questionnaire. The study protocol was approved by the Medical Ethics Committee (METC) of the VU University Medical Center and is described in greater detail elsewhere [80]. This RCT was part of the Depression Initiative, a national initiative to improve depression management in the Netherlands [23,81]. The study progress was monitored by a steering group and advisory board on a 3 monthly basis.

Collaborative Care

The intervention consisted of manual guided self-help, 6–12 sessions of Problem Solving Treatment (PST), a workplace intervention and if considered necessary, antidepressant medication. The OP-care manager and the consultant psychiatrist comprise the team. PST is a structured brief psychological intervention, aimed at teaching the employee problem solving skills [82]. In the workplace intervention the OP-care manager, the employee and employer highlight barriers for RTW, brainstorm for potential solutions regarding going back to work and clearly define a plan for implementing these solutions. Communication followed existing Dutch laws and guidelines [83] as in these meetings only the barriers and solutions for going

back to work were addressed and not the psychological complaints and diagnoses. The elements of the intervention ran parallel to each other. Every 2 weeks, treatment progress was monitored, and if necessary, was intensified by adding extra sessions PST, by adding antidepressant medication to the treatment plan or by increasing or changing the antidepressant medication. If symptoms were persistent after 18 weeks of treatment, the employee was referred to secondary mental health care. OP-care managers received a training of 2.5 day in collaborative care, and were supported by a web-based tracking system to monitor and follow the protocol, and by a psychiatrist for possible consultation. The OP-care managers received training regarding PST and the workplace intervention, from researchers that were trained by the developers of collaborative care, the IMPACT research group in Seattle.

Care as Usual

Dutch employees visit their company's OP in the first 6 weeks of their sickness absence. A company's OP is supposed to operate according to the OP guidelines of the Dutch Board of Occupational Medicine [84]. However, there is known to be a high fluctuation in the care that is actually delivered. In the care as usual group, the OP received no extra training and after 1 year, actual care delivered was assessed by questionnaire.

Data Collection and Outcome Measures

Data was collected at 3 months interval by the Netherlands Institute of Mental Health and Addiction (NIMHA). The follow-up was 1 year and measurements took place at baseline (T0) and after 3 (T1), 6 (T2), 9 (T3) and 12 (T4) months. The sent questionnaires were anonymously processed by researchers, meaning that they were essentially blinded and that all confidential information was treated according to the medical confidentiality rules and employees' names were coded. Cost-utility was determined by calculating, the medical costs, the productivity costs and the quality of life. The Trimbos/iMTA questionnaire for costs associated with psychiatric illness (TiC-P) [85] and the EuroQol (EQ5D) [10] were respectively used. Finally, cost-utility was expressed in cost per QALY.

Quality of Life

We applied the EuroQol (EQ5D) to estimate the utilities [10]. This generic health index is a standardized, validated instrument and encompasses five dimensions:

mobility, self-care, usual activities, pain/discomfort, and anxiety/ depression. Each dimension is rated by the patient on three levels (no problems, some problems, and extreme problems). Thus, 243 distinct health states are defined, each with a unique utility score, ranging from 1 (perfect health) to 0 ('death'). The health descriptions were linked to empirical valuations of the Dutch general public, allowing utilities to be computed. To obtain one utility score per employee, the area-under-the curve method (AUC) was applied [11].

Health Care Utilization Costs

Part 1 of the TiC-P is a validated instrument that measures the healthcare costs by measuring the number of contacts with health care services during the last 3 months, which can then be multiplied by the reference unit prices of 2009 of these services [86].

Productivity Costs

The second part of the TiC-P contains the SFHLQ [87]. This part questions about productivity losses that are caused by absenteeism and presenteeism. Productivity losses were valued according to the average value added per worker by age and gender per day and per hour. If respondents indicated that they had been absent for the entire recall period, data were collected from the time when the period of long-term absence started. This additional information was used to value the production losses according to the ''friction cost method'' [14]. This method takes into account the economic circumstances that limit the losses of productivity to society, which are related to the fact that a formerly unemployed person may replace a person who becomes disabled. Sickness absence for less than 1 month was defined as short-term absence and sickness absence for more than 1 month as long-term absence.

Incremental Cost-Effectiveness Ratio

An incremental cost-effectiveness ratio was calculated to obtain the costs per Quality Adjusted Life Year (QALY). The incremental cost-effectiveness ratio was calculated by dividing the incremental costs by the incremental effects, by the following formula (3.1).

$$\frac{<Costs_{cc}> - <Costs_{cau}>}{<Effect_{cc}> - <Effect_{cau}>} \quad (3.1)$$

$< Costs_{cc} >$ =Mean costs per patient in collaborative care
$< Costs_{cau} >$ =Mean costs per patient in care as usual
$< Effect_{cc} >$ =Mean effect per patient in collaborative care
$< Effect_{cau} >$ =Mean effect per patient in care as usual

Cost-Utility Analyses

Analyses were conducted using Statistical Package for the Social Sciences 19.0 (SPSS 19.0) [88], Excel 2010 and Statistical Analysis System 9.2 software (SAS 9.2). Copyright [2002–2008] SAS Institute Inc SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

First, the healthcare costs and quality of life scores were calculated by SPSS and normalized using BoxCox transformations and power transformations [89]. Because of the extremely high skewness in the productivity costs, it was not possible to normalize them by time unit, so we normalized the total. Next, the missing values in productivity costs, healthcare costs and quality of life scores per time unit were imputed with a Markov Chain Monte Carlo Multiple Imputation in SAS. Different variables, like scores of the PHQ9, age and gender were included to get a better estimate. There was a backwards transformation of productivity costs, healthcare costs and quality of life scores. As data was first normalized by a formula, we used the inverse to apply the backward transformation. The uncertainty in the analysis was assessed using bootstrapping in Excel, with 10 000 iterations. This was expressed in a cost-effectiveness plane.

3.3 RESULTS

Participants and Baseline Characteristics

At baseline, 126 employees were included, who had been absent for 4–12 weeks: 65 employees were randomized in the collaborative care group and 61 in the care as usual group. Table 3.1 summarizes the baseline demographic and clinical employees' characteristics for the care as usual group and collaborative care group. No significant differences between them were found.

Table 3.1| Baseline characteristics

	Collaborative care (n=65)	Care as usual (n=61)
Age (years)	41.9 (SD=11.4)	43.4 (SD=11.4)
Gender (% male)	46.2	45.9
Marital status (% single)	26.1	19.7
Dutch nationality (%)	95.4	91.8
Depressive symptoms (PHQ9, range 0 to 27)	16.1 (SD = 5.4)	15.9 (SD = 4.9)
Quality of life (range 1 to 1)	0.60 (SD=0.21)	0.56 (SD=0.27)
Paid work (n)	62	60

Quality of Life

The scores at baseline did not differ significantly between both groups. The quality of life scores improved significantly over time for both groups (care as usual 0.16 (95% CI 0.11–0.19) and collaborative care 0.11 (95% CI 0.07–0.14)), see Table 3.2, but the difference in improvement of 0.05 QALY between both groups was not significant (95% CL 0.00 to 0.11).

Table 3.2| Mean utility scores (SD)

	Collaborative care (n = 65)	Care as usual (n = 61)
Baseline	0.60 (0.21)	0.56 (0.27)
After 3 months	0.67 (0.22)	0.70 (0.20)
After 6 months	0.73 (0.17)	0.73 (0.15)
After 9 months	0.75 (0.19)	0.77 (0.19)
After 12 months	0.77 (0.17)	0.80 (0.18)

Health Care Costs

The average health care costs were about €3,900 for the collaborative care group, compared to nearly €4,600 for the care as usual group. Mental health care was responsible for the largest part of the costs, see Table 3.3.

Table 3.3| Average cost per year of health care providers based on 2009 unit prices

	Collaborative care				Care as usual			
	Mean costs (SD)*	Costs (%)	Mean contacts	% using the service	Mean costs (SD)*	Costs (%)	Mean contacts	% using the service
GP	€251 (234)	9.1	4.5 (4.2)	70.1	€261 (231)	7.2	4.7 (4.1)	82.0
Mental health care institute	€740 (2,900)	26.8	4.3 (16.9)	26.2	€766 (1,589)	21.1	4.5 (9.2)	34.4
Private psychologist/ psychiatrist	€482 (613)	17.5	5.5 (7.0)	53.8	€594 (696)	16.4	6.8 (7.9)	59.0
Psychologist/ psychiatrist	€189 (1,076)	6.9	1.2 (6.4)	7.7	€187 (817)	5.2	1.2 (4.8)	13.1
OP	€238 (175)	8.6	4.2 (3.1)	73.8	€260 (225)	7.2	4.6 (3.9)	80.3
Specialist	€118 (227)	4.3	1.3 (2.5)	32.3	€81 (136)	2.2	1.2 (1.6)	45.9
Paramedic	€99 (207)	3.6	2.8 (5.8)	27.7	€159 (305)	4.4	4.4 (8.5)	39.3
Social worker	€76 (225)	2.8	1.2 (3.5)	12.3	€64 (180)	1.8	1.0 (2.8)	18.0
Alternative medicine	€76 (220)	2.8	1.4 (4.0)	15.4	€31 (99)	0.9	0.6 (1.8)	14.8
Selfhelp group	€11 (63)	0.4	0.2 (1.2)	0.0	€75 (278)	2.1	1.4 (5.3)	11.5
Day care	€0 (0)	0.0	0.0 (0.0)	0.0	€505 (1,757)	13.9	3.8 (12.1)	13.1
(Psychiatric) hospital days	€232 (1,721)	8.4	0.1 (0.7)	0.0	€600 (4,187)	16.5	1.6 (11.4)	4.9
OP care manager	€208 (246)	7.5	3.7 (4.3)	49.2	€0	0.0	0.0 (0.0)	0.0
Medication	€37 (69)	1.3	–	71.0	€43 (77)	1.2	–	77.0

GP general practitioner, OP occupational physician

*The sum of the mean costs of health care providers is not equal to the average total costs. This is because multiple imputation was performed on the costs after calculating the total costs on different points in time

Productivity Costs

Over time the percentage of employees having presenteeism and the percentage of employees experiencing absenteeism regarding long-term absence remained the same for both groups. However, absenteeism regarding short-term absence decreased for both groups. Summarized: both treatments did not have any effect on absenteeism regarding long-term absence and presenteeism and although absenteeism regarding short-term absence decreased over time in both groups, there was no difference in decline between the groups. The mean productivity costs for the care as usual group were €11,627 (SD = 18,744) and for the collaborative care group €10,110 (SD = 11,444). The costs for absenteeism and presenteeism were respectively €1,654 (SD = 2,656) and €10,806 (SD = 19,465) for

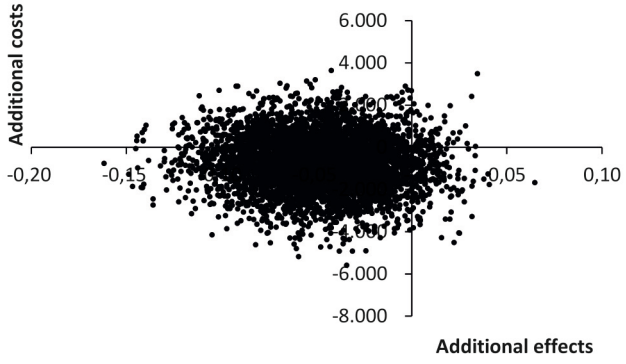
the care as usual group and €1,347 (SD = 1,465) and €8,853 (SD = 12,290) for the intervention group. The summation to the costs is not exactly equal to the total costs due to imputation.

Incremental Cost-Effectiveness Ratio

The average quality of life years (QALY's) gained was higher in the care as usual group (-0.05 (95% CI -0.11 to 0.00). The healthcare costs were €3,874 (95% CI €2,778– €5,718) in the collaborative care group and €4,583 (95% CI €3,108– €6,794) in the care as usual group. This lead to an incremental cost-effectiveness ratio (ICER) of 14,589 Euro/QALY.

The uncertainty in the data was presented in the cost-effectiveness plane in Fig. 3.1. The majority of the incremental cost-effect ratio (69%) falls in the south-west quadrant of the incremental cost-effectiveness plane, demonstrating that collaborative care is less costly but also less effective than care as usual. 27% of the cost-effect ratio falls in the north-west quadrant, indicating that collaborative care is inferior, meaning, it is more expensive and less effective than care as usual. Only 3% of the ratio's fall into the south-east quadrant and 1% in the northeast quadrant, respectively meaning a combination of higher effectiveness and fewer costs (dominant) and a combination of more effects and more costs for collaborative care compared to care as usual. Including the productivity costs did only slightly change the outcome of the analysis: 75% of the costs now fall in the south-west quadrant, 21% into the north-west quadrant, 3% in the south-east quadrant and 1% in the north-east quadrant.

Fig. 3.1| Cost-effectiveness plane of the additional health care costs and effects



Sensitivity Analysis

A sensitivity analysis was performed on admission to (parttime) day care and admission to psychiatric hospital. These costs were relatively high in the care as usual group but the number of contacts was relatively low. Omitting these costs did not affect the outcome of this study. There was only a slight change in the incremental costs per QALY. In addition, the majority of the cost-effect ratio's (70%) still fall in the southwest quadrant, 24% fall into the northwest quadrant, 4% in the southeast quadrant and 2% in the northeast quadrant.

3.4 DISCUSSION

This study is the first cost-utility analysis comparing collaborative care to care as usual for MDD in the occupational healthcare setting. The lower costs and lower effects in the collaborative care group, compared to care as usual, lead to an ICER of €14,589 per QALY. Collaborative care was less expensive compared to care as usual, mainly caused by lower healthcare costs; however this was at cost of quality of life gain. So, acceptance of our collaborative care intervention in the occupational healthcare setting is not to be expected for this particular diagnosis and for this particular study population. It is interesting that in this study, the costs of collaborative care were lower than the costs of care as usual, and that, as shown by Vlasveld et al [29], the severity of depressive symptoms did not differ between both groups. However, quality of life in the care as usual group increased more than in the collaborative care group, and although this difference was not significant, the combination of costs and effects resulted in an ICER that is called questionable. In the incremental cost-effectiveness plane, the large majority of the incremental cost-effect ratio fell in the quadrants of 'fewer costs, but less effective' and 'higher costs and less effective'. Exploring the incremental cost-utility for the total costs (thus, the inclusion of the productivity costs as well) resulted in comparable findings.

The differences in the healthcare costs were mainly due to higher costs for admission to a (parttime) hospital and admission to a psychiatric hospital in the care as usual group compared to collaborative care. However, the number of people that received such care was too low, to draw any conclusions. The sensitivity analysis showed that these costs did not have a large effect on the ICER. The collaborative care group did have higher costs concerning the OP-care manager, but the total costs remained lower in the collaborative care group. As expected, since the duration until return to work did not differ significantly between both groups, no difference was observed in reduction in absenteeism and presenteeism between both groups. This may be caused by the relatively low number of respondents in the study. Consistently, the productivity costs did not differ much between both groups. As discussed earlier, symptom reduction does not automatically lead to return to work and therefore it is interesting to look at the different aspects that are of influence. Studies already showed that even if care as usual and the intervention under study effect psychological symptoms to

the same extent, return to work can be effected differently [90-93]. Applying the biopsychosocial model, sickness absence and return to work not only depend on a health condition, but can be explained by a number of different factors (like personal characteristics, the environment, the workplace, the compensation system and the healthcare delivery system) [94,95]. More research should be conducted to identify these associated nonmedical factors [96,97].

Over time, the quality of life improved in both groups, but the quality of life in the care as usual group increased more, although this effect was not significant. This finding corresponds with the results of the Vlasveld et al.[29] regarding the 9 item depression subscale of the Patient Health Questionnaire (PHQ9), a continuous outcome measure. In this study, it was argued that the increased response in the collaborative care group might have influenced the quality of life in the collaborative care group, without having an effect on return to work. In our study, no such effect was found.

A number of important limitations need to be considered. Only two-thirds of the collaborative care group visited the OP care manager and almost no one received the workplace intervention [29], which narrows the contrast between the collaborative care group and the care as usual group. This may be caused by the waiting lists that came into existence as many employees entered the study concurrently. Secondly, because some employees in the collaborative care group already received psychological treatment, it is also possible that some employees found the additional collaborative care treatment too intensive, which may have caused a lower quality of life and subsequently an increased ICER. Thirdly, because of the separation of treatment and sickness certification in the Dutch legislation, employees may not be used to the treatment role of the OP–care manager. With respect to the workplace intervention, they may have felt uncomfortable to have meetings with their employer and OP-care manager together. According to a recent report of the OECD that pleads for more integration of the occupational and mental health care system occupational care can be improved by an increased collaboration between caregiver and employer [98].

Conclusion

This study has been unable to demonstrate the cost-utility of collaborative care in an occupational healthcare setting. Widespread implementation of collaborative

care in the occupational healthcare setting, as was operationalized in this study, is therefore not justified. Perhaps collaborative care in this setting may be (cost) effective when adjustments are made, for example in having the treatment administered by a different occupational healthcare professional including proper implementation of the workplace intervention. However, this should be examined in further research adapted to the Dutch occupational healthcare setting.

4 COST-UTILITY OF COLLABORATIVE CARE FOR MAJOR DEPRESSIVE DISORDER IN PRIMARY CARE IN THE NETHERLANDS

Based on: Goorden M., Huijbregts K.M.L., van Marwijk H.W.J., Beekman A.T.F., van der Feltz-Cornelis C.M., Hakkaart-van Roijen L. (2015). Cost-utility of collaborative care for major depressive disorder in primary care in the Netherlands. Journal of Psychomatic Research, 79(4): 316-23

Abstract

Objective: Major depression is a great burden on society, as it is associated with high disability/costs. The aim of this study was to evaluate the cost-utility of Collaborative Care (CC) for major depressive disorder compared to Care As Usual (CAU) in a primary health care setting from a societal perspective.

Methods: A cluster randomized controlled trial was conducted, including 93 patients that were identified by screening (45-CC, 48-CAU). Another 57 patients were identified by the GP (56-CC, 1-CAU). The outcome measures were TiC-P, SF-HQL and EQ-5D, respectively measuring health care utilization, production losses and general health related quality of life at baseline three, six, nine and twelve months. A cost-utility analysis was performed for patients included by screening and a sensitivity analysis was done by also including patients identified by the GP.

Results: The average annual total costs was €1131 (95% C.I., €−3158 to €750) lower for CC compared to CAU. The average quality of life years (QALYs) gained was 0.02 (95% C.I., −0.004 to 0.04) higher for CC, so CC was dominant from a societal perspective. Taking a health care perspective, CC was less cost-effective due to higher costs, €1173 (95% C.I., €−216 to €2726), of CC compared to CAU which led to an ICER of 53,717 Euro/QALY. The sensitivity analysis showed dominance of CC.

Conclusion: The cost-utility analysis from a societal perspective showed that CC was dominant to CAU. CC may be a promising treatment for depression in the primary care setting. Further research should explore the cost-effectiveness of long-term CC.

4.1 INTRODUCTION

MDD was ranked fourth in the list of diseases that cause the highest burden of disease in 2002, and in 2030 it is expected to be ranked second worldwide and first in high-income countries [99]. The costs associated with MDD, especially the costs for society, are high [5,18]. The productivity costs attributable to MDD amount to €242 per worker per year [17] and on average account for 60–70% of the total costs associated with depression [5,18].

Research into interventions that reduce the societal burden of MDD is therefore of paramount importance. A promising treatment for MDD is the collaborative care model [100-103] that is based on the World Health Organization (WHO)'s chronic care model. This system intervention aims to increase collaboration between health care professionals and patients, and actively monitors patients' prognoses. A recent study in the Netherlands [26] showed that for patients with MDD, CC is more effective at 3 months (response to treatment 41.9% CC group; 10.5% CAU group). This study compared Collaborative Care (CC) to Care As Usual (CAU) over one year in the primary care setting, including organizational measures, such as introducing a nurse-care manager in primary care, providing Problem Solving Treatment (PST), guided self-help, progress monitoring of the patient and structural availability of a consultant psychiatrist, as well as a web-based provider decision support system. There is an increasing role of economic evaluations in health care decision-making [32]. A review on the economics of CC for depression by Jacob et al. (2012) indicates that CC provides good economic value[31]. Another review of the cost-effectiveness of CC showed that CC was associated with high clinical benefits at a low increment in health care costs for older adults [32]. The estimated gains in Quality Adjusted Life Years (QALY) in this review were between 0.02 and 0.12. However, the quality of the studies in this review, as measured by the Consensus on Health Economic Criteria (CHEC) list[104], was low, and the studies had a maximum follow-up period of only 6 months. Another drawback of existing work is that production losses, which are responsible for more than 60% of the societal costs associated with depression, are often not included [18,32]. A recent study by Green et al. (2014)[30], who assessed the cost-effectiveness of collaborative care in a UK primary setting, indicated that collaborative care gained more effect at relatively low costs. Another recent study conducted in Spain [105], which did include productivity costs in their cost-effectiveness analysis, indicated that CC in primary care for depression

was only slightly more expensive and induced a larger effect (0.045 QALY). However, the governmental perspective that was adopted was narrow and the costs for presenteeism were not included. In general, the cost-utility studies pertaining to CC for depression were conducted in the United States. This might affect generalizability of studies to other countries or health care systems. In the Netherlands, for instance, GP practices are most often small business units (1–5 GPs per practice, mean 2) with their own culture and rules [106,107]. In addition, in the Dutch health care system, as in the UK, the GP acts as the gatekeeper who refers patients to other professionals [108]. In the USA, primary care practices are generally centrally organized units that are relatively large, and have some form of central regulation in terms of availability of treatment and reimbursement. Specific aspects of differences between the USA primary care situation and the primary care situation in the Netherlands in relation to the development of the CC model are described extensively elsewhere [27].

This study is the first cost-effectiveness study in the Netherlands for CC that is taken from a societal perspective. The higher expected effect of treatment in this study is mainly captured through reduced workplace absences and not through reduced health care expenses for other health care providers.

Usual care for major depression in primary care in the Netherlands includes prescription of antidepressants or referral to psychotherapy [109]. In the CC model, a depression care manager (DCM), usually a qualified nurse, collaborates with a GP and a liaison psychiatrist in order to provide and guideline more structured and adherent depression treatment in primary care. Forty per cent of patients with a diagnosis of a current depressive or anxiety disorder in the primary care setting requesting treatment are treated in accordance with clinical guidelines [110]. Guideline adherence is significantly associated with increased care use but also with corresponding costs [109]. We therefore expect the costs that are associated with CC to be higher compared to usual care. However, as the effect of treatment is also expected to be higher compared to CAU, the additional costs for other health care providers may decrease over time causing the intervention to be cost-effective or even dominant. Dominance indicates a combination of lower costs and higher effects for the treatment under study.

The primary objective of this paper was to assess the cost utility of CC in primary

care compared to CAU for MDD in the Netherlands. In the Netherlands, it is compulsory that a cost-effectiveness analysis is performed from a societal perspective, meaning that not only direct medical costs but also productivity costs due to absence from work and presenteeism are taken into account.

4.2 METHODS

Randomization and recruitment

The cost-utility analysis was conducted along a cluster-randomized controlled trial (RCT), evaluating the effectiveness of CC versus CAU in the primary care setting. Results of this RCT on the effectiveness of CC and design and methodological details of this study have been described elsewhere [26,111]. Computer-generated randomization took place at the level of 18 primary care centers. Each general practice randomized to the CC condition assigned a practice nurse; the DCM. Patients of the respective practices could enter the trial in two ways: either by screening or after identification by their GP. These two ways were used in order to keep selection bias as low as possible. In this study, in order to evaluate possible differences between the group selected by screening and the group selected by the GP, a sensitivity analysis was performed. Screening was done as follows: patients who had consulted the GP in the past six months received the Patient Health Questionnaire [112] (the PHQ-9), and were asked for informed consent by mail. If they scored screen-positive (PHQ9 score ≥ 10), the Mini-International Neuropsychiatric interview (MINI) was administered by telephone. If patients were classified with MDD according to the MINI and were over 17 years old, they were included. Patients were excluded if they were suicidal as established during the MINI and a subsequent doctor interview, had psychotic symptoms, suffered from dementia, drug or alcohol dependence, had insufficient mastery of the Dutch language or if they were already under specialty mental health treatment, as the trial provided treatment in primary care.

Study oversight

The study protocol was approved by the Medical Ethics Committee (METC) of the VU University Medical Center (protocol number 2006/ 158). This RCT was part of the Depression Initiative, a national initiative to improve depression management in the Netherlands [23]. The study was monitored by the Board every three months.

Interventions

CC

The integrated intervention consisted of problem solving treatment (PST), manual guided self-help, and, if necessary, antidepressants. The DCM provided manual guided self-help (ZHM) and PST, and the GP prescribed antidepressant medication. Remission (PHQ9 b 5) after 18– 24 weeks of treatment was the target. Every two weeks monitoring by PHQ9 checked if the score had dropped at least 5 points; if this was not the case, a switch to more intensive treatment, like adding antidepressant medication to PST (or switching to other medication or increasing the dosage of the antidepressant), was advised. The DCM discussed the progress of the patients with the GP and consulted the GP if medication issues would arise. At the occurrence of adverse events, suicidality, or lack of progress, or if remission was not achieved between 18 and 24 weeks and referral to specialty mental health care was seriously considered, the consultant psychiatrist would be consulted. The care manager, the GP and the consultant psychiatrist all had access to a web-based tracking system to monitor and follow the protocol. The web-based tracking system is a secured website with a separate file for each patient. This is accessible to the care manager, the GP and the consultant psychiatrist of the patient. The tracking system instructs the care manager about the steps that need to be taken according to the collaborative care treatment algorithm. If the care manager fails to follow important instructions within a set time period, the consultant psychiatrist and the researchers are notified by e-mail. The researchers also use this information during their weekly phone calls with the care manager, in which the researcher stimulates adherence to the collaborative care protocol. Furthermore, every six weeks a meeting with other care managers is organized for PST supervision based on PST sessions that have been audiotaped with patients' permission.

GPs in primary care centers randomized to the CC condition received training in the CC model, the use of the web-based tracking system and got acquainted with the consultant psychiatrist. DCMs received training and supervision in PST, training in the guided self-help manual and in the monitoring and use of the tracking system.

CAU

Patients recruited in the control condition were informed by the research assistant after the MINI interview that they might be depressed and were advised to seek treatment from their GP, if they did feel the need to. There were no restrictions to treatment in any way. The GPs in the control condition were not informed about the presence of MDD in screened patients. Actual treatment as provided in both treatment conditions was monitored by TIC-P.

Data collection and outcome measures

Data was collected at 3 month intervals by the Netherlands Institute of Mental Health and Addiction (NIMHA or Trimbos-instituut). The follow-up was one year and measurements took place at baseline (T0) and after three (T1), six (T2), nine (T3) and twelve (T4) months. All confidential information was treated according to the medical confidentiality rules and patients' names were coded. Cost-utility was determined by calculating the medical costs, the productivity costs and the quality of life. The incremental costs and outcomes of these interventions were used to assess cost-effectiveness. The Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P) [13] and the EuroQol (EQ-5D) [10] were respectively used.

Quality of life

We applied the EuroQol (EQ-5D) to estimate utilities. We applied the Dutch tariff to calculate the utilities [113]. This generic health index is a standardized, validated instrument and encompasses five dimensions: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. Each dimension consists of three levels: no problems, some problems and extreme problems, therefore defining a total of 243 different health states.

Health care utilization costs

Part 1 of the TiC-P is a validated instrument that measures the direct medical costs by measuring the number of contacts with health care services (general practitioner (GP), psychiatrist, medical specialist, physiotherapist, alternative health practitioner, day care/hospital length of stay, and medication) during the last three months, so we can extract the costs by multiplying them by the reference unit prices of 2009 of these services [86]. Also, information about psychotropic medication (amount, frequency and type of substance) was collected.

All prices were indexed to 2013. Costs of the mental health care practice nurse were based on the fees and time comparable with the costs of a general practitioner and subsequently used in the analysis.

Productivity costs

The second part of the TiC-P contains the SF-HLQ. This part questions about productivity losses that are caused by absence, reduced efficiency at work and difficulties in job performance. Sickness absence for less than one month was defined as short-term absence and sickness absence for more than one month as long-term absence. If respondents indicated that they had been absent for the entire recall period, data were collected from the time when the period of long-term absence started. This additional information was used to value the production losses according to the friction cost method [14]. This method takes into account the economic circumstances that limit the losses of productivity to society, which are related to the fact that a formerly unemployed person may replace a person who becomes disabled. Productivity losses were valued according to the average value added per worker by age and gender per day and per hour.

Statistical analysis

Analyses were conducted using Statistical Package for the Social Sciences 19.0 (SPSS 19.0), Statistics and data (Stata 8.0 se) and Excel (2010). First, the direct costs, productivity costs and quality of life scores were calculated by SPSS. Missing values in direct costs and quality of life scores per time unit were modeled and imputed with chained equations in Stata. The productivity costs were not imputed but considered to be zero when missing. The costs were extracted by multiplying the number of contacts by the reference unit prices of 2009 of these services[86]. To obtain a utility score per patient, the area-under-the curve method (AUC) was applied [11]. This method consists of linearly interpolating between the different health states at the different time points. Subsequently, the area under the curve is calculated.

To account for the skewedness in the dataset, predictive mean matching was used. This method imputes missing values by means of a donor from the nearest neighbor with a distance based on the expected values of the missing variables given the observed covariates. It is therefore more robust against skewed data. 10 imputed datasets were created. Different baseline variables, like age and gender

were included to get a better estimate. The incremental cost-effectiveness ratio (ICER) was calculated to obtain the costs per Quality Adjusted Life Year (QALY). The incremental cost-effectiveness ratio was calculated by dividing the incremental costs, consisting of the direct and productivity costs, by the incremental effects. As the data was skewed, the uncertainty in the analysis was assessed using bootstrapping in Excel, with 20,000 iterations. This was expressed in a cost-effectiveness plane and a cost-effectiveness acceptability curve. In the cost-effectiveness plane, both incremental costs and incremental utilities are plotted to account for combinations. These combinations fall into different parts of the plane. If they, for instance, fall into the northeast quadrant, it means that CC generates more utilities but also higher costs. If the costs and utilities fall into the southeast quadrant, it means that it is less costly and gains more utilities. This intervention is then called dominant. Another way to present uncertainty is the cost-acceptability curve. This curve illustrates the probability that the ICER will be accepted for different cost limits.

Firstly, we assessed the groups of patients in the CAU group and the CC group that were selected by screening. Subsequently, a univariate sensitivity analysis was performed that also included patients identified by the GP in the analysis in order to ascertain if this yielded differences in terms of cost-utility.

4.3 RESULTS

At baseline, 9 primary care centers were randomized to the intervention condition and 9 centers to the control condition. 150 patients were included; 49 patients (1 patient identified by the GP and 48 screened patients) were randomized to the CAU condition and 101 patients (56 patients identified by the GP and 45 screened patients) were randomized to the CC condition. Respectively after three, six, nine and twelve months 68.9%, 68.9%, 62.2% and 73.3% in the CC group returned their questionnaires. For the screened CAU group, 77.1%, 79.1%, 62.5% and 64.6% returned their questionnaires. Table 4.1 summarizes the baseline demographic characteristics for the screened groups. There were no significant differences between both groups.

Table 4.1| Characteristics of the patients in the screened Collaborative Care groups and the screened Care As Usual group.

Characteristics	Collaborative Care screened (N = 45)	Care As Usual screened (N = 48)
Age in years (SD)	52.0 (13.0)	53.0 (14.2)
Gender (% female)	66.7	72.9
Living alone (% widowed/divorced or unmarried)	53.3	52.1
Origin (% Non Dutch origin)	22.7	25.5
Level of education* (SD)	5.4 (2.5)	5.2 (3.0)
Quality of life at baseline (T0) in QALY (SD)	0.54 (0.25)	0.56(0.25)
Depression in past (% prior episode)	58.5	57.4
Severity, PHQ-9 score (SD)	14.3 (4.8)	14.8 (4.8)
Comorbidity chronic disease (% comorbidity)	45.6	42.9
Likelihood of comorbid somatoform disorder' according to 4DSQ (% high likelihood)	13.5	15.4
Likelihood of a comorbid anxiety according to 4DSQ (% high likelihood)	27	17.5
Paid job (% yes)	46.7	48.9

*5 corresponds to only secondary school; 6 corresponds to a few years of education following secondary school.

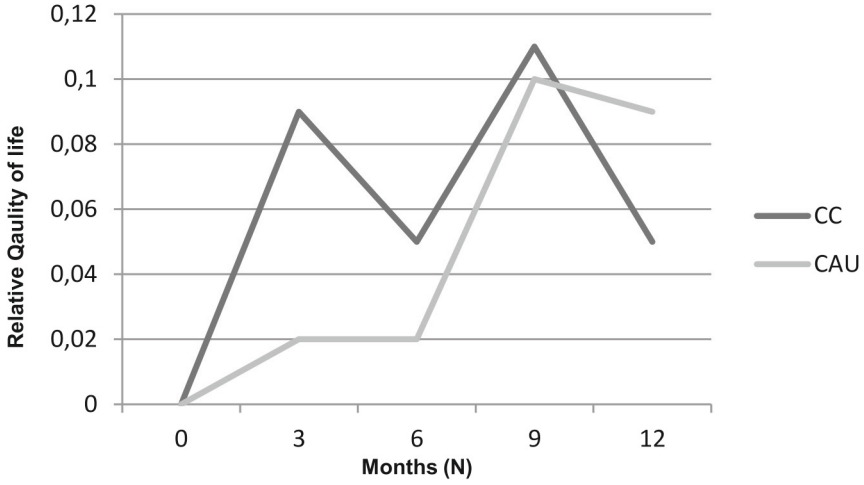
Quality of life

Quality of life scores were imputed on different points in time. After the area under the curve was calculated, both groups improved significantly over time; 0.05 (95% C.I., 0.03 to 0.06) QALY for the CAU group and 0.07 (95% C.I., 0.05 to 0.09) QALY for the CC group but there was no significant difference in improvement over time between both groups 0.02 (95% C.I., −0.004 to 0.04) QALY. The aggregated values and the relative values (in respect to baseline) of the quality of life data over time are shown in Table 4.2 and plotted in Fig 4.1.

Table 4.2| Quality of life at baseline, after 3, 6, 9 and 12 months for both groups.

	Collaborative Care screened (N = 45) Mean quality of life (SD)	Care As Usual screened (N = 48) Mean quality of life (SD)
Baseline	0.54 (0.25)	0.56 (0.25)
After 3 months	0.63 (0.25)	0.58 (0.30)
After 6 months	0.59 (0.29)	0.58 (0.25)
After 9 months	0.65 (0.26)	0.66 (0.25)
After 12 months	0.59 (0.27)	0.65 (0.26)

Fig. 4.1| Relative quality of life over time respectively to baseline (area under the curve is the difference of surface between the lines).



Health care utilization costs

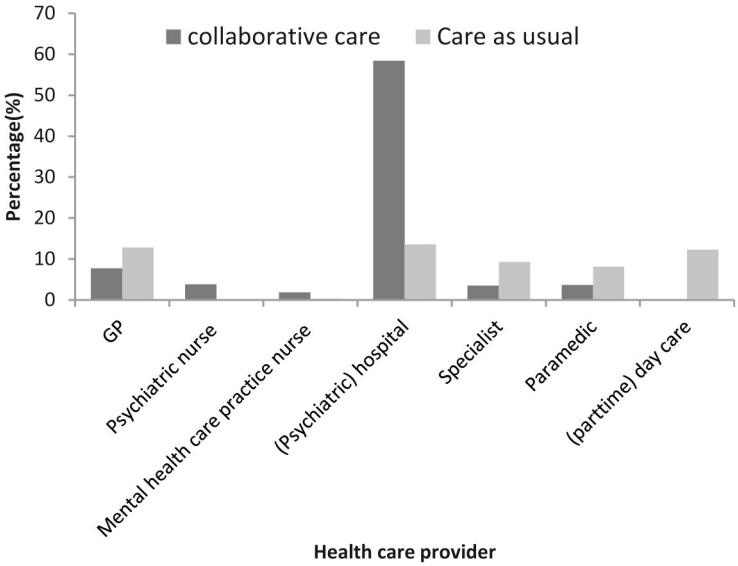
The average direct medical costs were €4011 (95% C.I. €2679 to €5513) for the screened CC group compared to €2838 (95% C.I. €2463 to €3244) for the CAU group, see Table 4.3 . The costs that made up the largest part of the total costs are presented in a bar chart, see Fig. 4.2. There was no information available for the contacts with the psychiatric nurse in the CAU group. For further analysis we have set these costs to zero.

Table 4.3| Average cost per year regarding to specific health care providers, percentage of costs, mean number of contacts for patients with the health care provider and the percentage of people that visited the healthcare provider for the screened groups based on, Euro's, 2013.

	Collaborative Care Screened (N=45)[a,b]				Care as Usual Screened (N=48)[a,b]				
	Mean costs (SD)	Costs in Euro (%)	Mean number contact/ Days (SD)	Percen-tage of people (%)	Mean costs (SD)	Costs in Euro (%)	Mean number contact/ Days (SD)	Percen-tage of people (%)	Unit costs in euro (indexed)
General practitioner (GP)	326 (298)	7.7	5.3 (4.9)	83.7	288 (307)	12.8	4.7 (5.0)	89.1	61
Psychiatric nurse	148 (279)	3.8	2.0 (3.7)	39.0	No inf.	–	–	–	84
Mental health care practice nurse	52 (139)	1.9	1.0 (2.5)	15.9	5 (32)	0.3	0.1 (0.7)	2.0	61
Admission (psychiatric) hospital	2464 (15645)	58.4	5.4 (34.3)	4.7	304 (1106)	13.6	0.6 (2.2)	15.2	c
Mental Health Care Institute (RIAGG)	247 (534)	5.9	1.3 (2.9)	23.3	599 (2181)	26.7	3.2 (11.7)	26.1	186
Private psychologist/ psychiatrist	178 (415)	4.2	1.9 (4.3)	30.2	90 (283)	4.0	0.9 (3.0)	19.6	96
Psychologist/ psychiatrist at Outpatient center of hospital	154 (783)	3.6	0.9 (4.2)	11.6	61 (206)	2.7	0.3 (1.1)	10.9	d
Occupational physician (OP)	35 (107)	0.8	0.6 (1.7)	23.3	49 (115)	2.2	0.8 (1.9)	21.7	62
Specialist	147 (192)	3.5	1.4 (1.8)	55.8	208 (289)	9.3	2.0 (2.8)	54.3	105
Paramedic	156 (278)	3.7	4.0 (7.1)	46.5	183 (366)	8.1	4.7 (9.3)	39.1	39
Social worker	166 (372)	3.9	2.3 (5.3)	25.6	57 (151)	2.5	0.8 (2.1)	19.6	71
Counseling center for drugs alcohol e.a.	0 (0)	0.0	0.0 (0.0)	0.0	2 (13)	0.1	0.1 (0.4)	2.2	30
Alternative medicine	60 (192)	1.4	1.0 (3.2)	20.9	56 (159)	2.5	0.9 (2.7)	17.4	60
Selfhelp group	0 (0)	0.0	0.0 (0.0)	0.0	4 (25)	0.1	0.1 (0.4)	2.2	57
(Parttime) day care	5 (34)	0.1	0.02 (0.2)	2.3	276 (1,833)	12.3	2.0 (13.7)	4.3	e
(Psychotropic) medication	39 (53)	0.9	–	88.4	40 (66)	2.9	–	82.6	–
Total costs	4011 (95% C.I. 2679 to 5513)				2838 (95% C.I. 2463 to 3244)				

a As there was some missing data that was not included in the frequency table, the percentage of patients will not always be a round number. b Because of imputation, the sum of the costs in Table 2 is not equal to the total costs.
c Academic hospital: €626; general hospital: €474; psychotherapeutical or psychiatric hospital: €253; other: €401.
d Academic hospital: €281; general hospital: €139 psychotherapeutical or psychiatric hospital: 188; other: €199.
e Academic or general hospital: €273; psychotherapeutical or psychiatric hospital: €167; other: €220.

Fig 4.2| Percentage of costs presented in a bar chart, for the screened groups.



Productivity costs

The mean days of absenteeism and presenteeism for CAU and CC are shown in Table 4.4. The total mean absences for respectively the CAU group and the CC group were 15.9 (SD = 79.4) and 7.7 (SD = 28.3) days. The costs of absence were €3671 (SD = 18,203) for the CAU group and €1347 (SD = €3878) for the CC group. For the CAU group the mean total days of presenteeism were 2.3 (SD = 4.8) and for the CC group they were 2.7 (SD = 4.7) days. At baseline, in the CAU group 21% of the patients was older than 65. In the CC group only 9% was older than 65. Despite patients in the CAU group working (slightly) less efficiently, as more patients were older than 65, the costs were slightly lower, €622 (SD = €1150) compared to CC, €643 (SD = €1316).Total average productivity costs were €1990 (95%: €1709 to €2280) in the CC group and €4294 (95%; €2777 to €6011) in the CAU group. The main part of the productivity costs (68% for the CC and 86% for the CAU group) was due to absence from work.

Table 4.4| Absenteeism and presenteeism for the CAU and the CC group.

	Collaborative Care screened (N = 45)	Care As Usual screened (N = 48)
Absenteeism (days) (SD)	15.9 (79.4)	7.7 (28.3)
Percentage of patients reporting absence (%)	7.2%	6.3%
Presenteeism (days) (SD)	2.7 (4.7)	2.3 (4.8)

Perspectives

Societal perspective

In the CC group, the average quality of life years (QALYs) gained was higher (not significantly) compared to the CAU group. Health care utilization costs were higher but productivity costs were lower in the CC group compared to the CAU group, resulting in lower total costs for the CC group compared to the CAU group, −€1131 (95% C.I., €−3158 to €750). An overview of these results is shown in Table 4.5. The majority of the incremental cost-effect ratios (86%) fall in the southeast quadrant of the incremental cost-effectiveness plane, showing that CC is less costly and gains more utilities than the CAU (dominant). 11% of the ratios fall into the northeast quadrant indicating that CC is more costly but also gains more utilities, see Fig. 4.3. The cost-effectiveness acceptability curve is plotted in Fig. 4.4. We see that at a threshold of 20,000 Euro/QALY the probability that the ratio is acceptable is more than 90%.

Fig 4.3| Cost effectiveness planes, societal perspective (left), health care perspective (right).

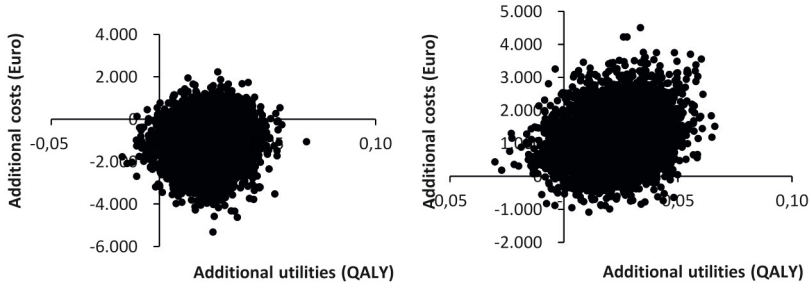


Table 4.5| Incremental costs, incremental utility and Incremental Cost Effectiveness ratio (ICER) for the screened groups from a societal and a healthcare perspective.

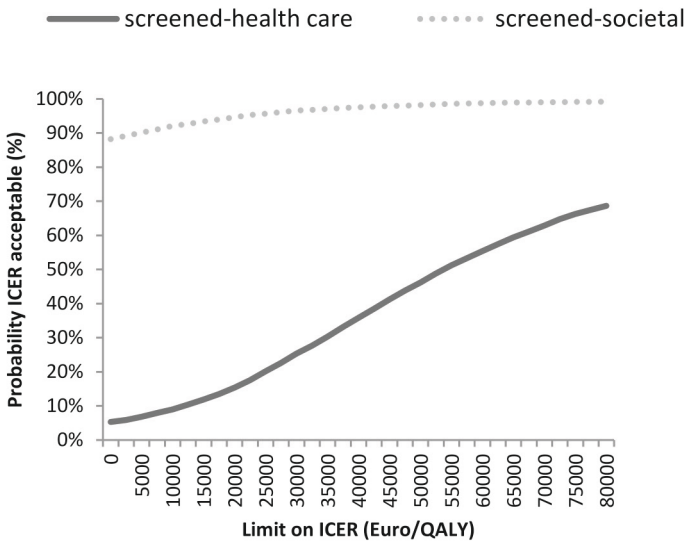
		Collaborative Care screened (N = 45)	Care As Usual screened (N = 48)
Societal Perspective	Average total costs	€6001 (95% C.I., €5051 to €7024)	€7132 (95% C.I. €5585 to €8898)
	Incremental utility	0.02 (95% −0.004 C.I., to 0.05)	
	ICER (Euro/QALY)	Dominant	
	Average direct medical costs	€4011 (95% C.I. €2679 to €5513)	€2838 (95% C.I., €2463 to €3244)
Healthcare perspective	ICER (Euro/QALY)	53,717	

Health care perspective

From a health care perspective, CC was more (but not significantly) expensive compared to CAU €1173 (95% C.I., €−216 to €2726) as now the productivity costs were not included. This lead to an ICER of 53,717 Euro/QALY. An overview of these results can be seen in Table 4.5.

Now, 90% of the ratios falls into the northeast quadrant, meaning that CC is more expensive but also gains more utilities. 5% of the cost-effectiveness ratios falls into the southeast quadrant, meaning that CC is more expensive and also gains less utilities. Finally, 4% of the cost-effectiveness ratios falls into the northwest quadrant, indicating that CC is more costly and also gains less utilities, see Fig. 4.3. In the acceptability curve (see Fig. 4.4), at a threshold of 20,000 the probability that the ratio is acceptable is around 20% and around 70% at a threshold of 80,000 Euro/QALY.

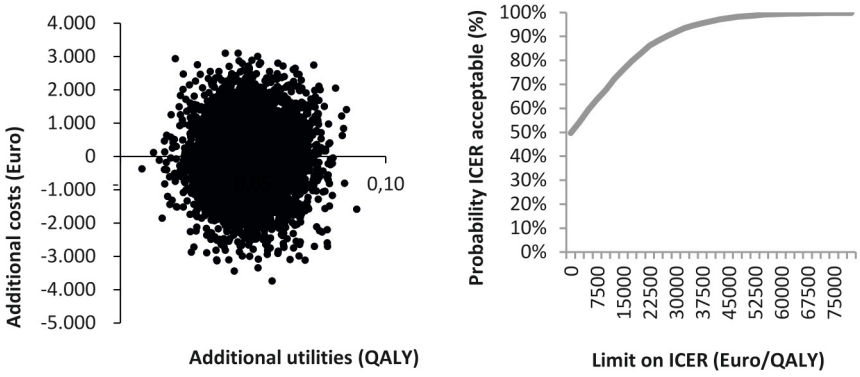
Fig 4.4| Cost-effectiveness acceptability curves



Sensitivity analysis: combined groups

Higher quality of life 0.05 (95% C.I., 0.03 to 0.07) and lower costs €316 (95% C.I., €−1189 to €2508) lead to a dominant cost-effectiveness ratio. The productivity costs in both groups were now similar (CAU: €4206 (SD = €17,956), CC €4206 (SD = €14,861)). Half of the incremental cost-effect ratio fall into the southeast quadrant (50%) meaning that CC is dominant, see Fig. 4.5 (left). The rest falls in the northeast quadrant of the incremental cost-effectiveness plane, indicating that CC is more costly but also gained more utilities than CAU. In Fig. 4.5 (right), we see that at a threshold of 20,000 Euro/QALY the probability that the ratio is acceptable was about 80%.

Fig 4.5| Sensitivity analysis cost-effectiveness plane (left) and cost acceptability curve (right)



4.4 DISCUSSION

This study is the first cost-utility analysis in the Netherlands comparing CC to CAU for MDD in the primary health care setting and showed CC to be a dominant intervention. The effect of the intervention vanishes when the intervention was finished as the quality of life at the end of the study was decreasing for the CC group. CC is dominant from a societal perspective, especially because of lower productivity losses due to absenteeism. From a health care perspective the results were less promising; as the CC was more expensive compared to CAU and the ICER increased to 53,171 Euro/QALY. This is reflected in the acceptability of the treatment which was now lower (around 20% at a threshold of 20,000 Euro/QALY and around 70% at 80,000 Euro/QALY).

In the main analysis, only screened patients were included. In the sensitivity analysis, also patients identified by the GP were added into the analysis (the total group). When the total group was considered, the incremental quality of life increased significantly which resulted in CC being a dominant intervention again.

In the main analysis, we choose not to include patients that were identified by the GP to avoid a selection bias. In the GP-identified CC group, GPs were involved in selecting patients, which resulted in a selection bias for this particular group for two reasons. Firstly, GPs in the CAU-group may not be motivated to select patients for the trial, as they did not feel like they had anything extra to offer to these patients. As a consequence, there was only one patient included in the GP-identified CAU group (this patient was not included in the analyses and we were unable to form a GP identified CAU group). Secondly, the GPs in the CC intervention received training, which might have contributed to their improved ability to detect patients. The comparison between the CC total group (with the GP identified CC patients) and the CAU group is therefore explorative. In our main analysis, all patients were blinded before inclusion, which allowed for an unbiased comparison between both groups. Further investigation is necessary to investigate the effects as selection by the GP may resemble everyday practice more closely.

As the patients in the CC group were in contact with a care manager (social worker, a psychologist, or a mental health care practice nurse), these costs were, as expected, higher compared to the CAU group. There was however no

information available about the contacts with the psychiatric nurse in the CAU group. As we expect these costs to be low, we do not expect them to have influenced our results. However, the other costs for health care services were all higher or the same in usual care when compared to CC, indicating that patients that do not have a care manager, relied on other resources. Hospital admission, which was expensive, was used by a relatively low percentage of patients. Also, the percentage is higher for the CAU group compared to the CC group (15.2% compared to 4.7% in the CC), but costs may be higher for CC group as the number of inpatient days was much higher (mean number of days is 5.4 for CC but 0.6 for the CAU group). Further investigation should investigate if there is an indirect association between CC therapy and hospitalization or visits to a rehabilitation center. It is important to determine these factors as the CC group identified by the GP will be more similar to patients in daily practice. As expected from other studies [5,18], the productivity costs accounted for a large amount of the total costs. It is therefore highly recommended that these costs are included, assessing cost effectiveness in a population of depressed patients generally in their working age.

The productivity costs in the screened groups were lower in the CC group when compared to the CAU group. This was mostly due to the lower costs of absence from work in the CC group. This effect vanished when in the sensitivity analysis, the total group was considered; there was no difference in productivity costs between both groups. This might be caused by an implicit selection bias of the general practitioner.

In agreement with the study of Green et al. (2014) [30], from a health care perspective, collaborative care was cost-effective with similar gains in QALY compared to our study (0.02). In the review of Steenbergen-Weijenburg et al. (2010) [32] of the cost-effectiveness of CC regarding major depressive disorders, the utilities gained were between 0.02 and 0.12 QALY. However, our study was associated with utilities on the lower bound of this spectrum (0.02 QALYs). This may be explained by the difference in time span of the studies in the reviews; the duration of the studies was six months while our study measured cost-utility over a year. Further research should indicate if this is due to decay in the effects of the intervention and if relapse prevention or longer treatment is necessary. A recent study of Aragones et al. (2014) [105], showed a difference of 0.045 QALY over a 1-year timespan between the CC group and the CAU group. It is possible that the

difference in effects is caused by differences in the intervention or differences in the setting (Spanish versus Dutch). More investigation is needed to expose the reasons. The small not significant increase in QALYs (especially in the first three months) corresponded with the study of Huijbregts et al. (2013) [26] regarding the PHQ9-score. However, although the increase in QALYs was small, as the ICER depends on both the gains in QALY and the costs, the costs have to be low for the ICER to fall into acceptable limits. Quality of life scores also showed less fluctuation over time for the CAU group compared to those for CC group. Further research is necessary to assess the reasons.

When the total group was considered, the study produced results that corroborate the findings of the study of Aragones et al. (2014) [105]. A possibility is that the GP-selected patients were more motivated for change, which caused the higher increase in quality of life.

The study had limitations and strengths. Firstly, there was a high percentage of non-response to the questionnaires that were sent by mail and the sample size was small. There may have been an unmeasured selection bias, but at baseline there was no difference in demographics between both groups. Secondly, travel costs and participant time were not taken into account, as there was no reason to assume that these costs would differ between the groups. Thirdly, the design of CC in this study was based on the design developed by Unutzer et al. (2001) [114]. However, contrary to their design, instead of 1-year CC treatment, treatment was only applied for 18–24 weeks to generate fast treatment response. Subsequently, response may be better maintained when treatment duration is increased. A stronger focus on maintaining response and remission may be an important issue for the future. Fourthly, there were also two deviations from the protocol. In the previously published protocol it was reported that patients would be included if they reached the cut-off score of 15 on the PHQ9. When screening the patients by using the cut-off point of 15, a more severe group of patients was included than we expected and other problems emerged, like addiction and psychosis that were not treated by the intervention. As we also used the MINI as inclusion criteria, we knew that everybody who was included had a diagnosis of depression according to the DSM-IV, so it seemed safe to lower the cut-off point to 10. In addition in the previously published protocol the calculated sample size was of 120 patients per group. Throughout the study, data from the English collaborative care trial became

available. The effect size was much higher than the effect size of the original power calculation. As healthcare in England is more similar to the Netherlands than compared to the United States, and they also used cluster randomization, we discussed this issue with our funding cooperation and subsequently they agreed that our N could be lowered. Fifthly, we did not adjust for baseline values in the cost-effectiveness study. However, this may not have impacted our results as there were no significant differences between the groups on baseline. Lastly, we did not use cluster analysis as our data was very skewed with a point mass at zero. However, as the Intra Cluster Correlation was 0.00 [26], this will not have influenced our results.

Collaborative care might be a promising intervention from a societal perspective. However, it is important to draw careful conclusions in light of the limitations of this study. In the first place the results are surrounded by uncertainty. Secondly, as the effect of the intervention subsided to a certain extent after 9 months. Further research should shed light on the identification of the characteristics of the patients that gain the most from collaborative care to improve cost effectiveness and decrease uncertainty when applying this relatively expensive therapy.

5 COST-UTILITY OF COLLABORATIVE CARE FOR THE TREATMENT OF COMORBID MAJOR DEPRESSIVE DISORDER IN OUTPATIENTS WITH CHRONIC PHYSICAL CONDITIONS. A RANDOMIZED CONTROLLED TRIAL IN THE GENERAL HOSPITAL SETTING (CC-DIM)

Based on: Goorden M., van der Feltz-Cornelis C.M., van Steenbergen-Weijenburg, K.M., Horn E.K., Beekman A.T.F., Hakkaart-van Roijen L. (2015). Cost-utility of collaborative care for the treatment of comorbid major depressive disorder in outpatients with chronic physical conditions. A randomized controlled trial in the general hospital setting (CC-DIM). Neuropsychiatric Disease and Treatment 13: 1881-1893.

Abstract

Objective: Major depressive disorder (MDD) is highly prevalent in patients with a chronic physical condition, and this comorbidity has a negative influence on quality of life, health care costs, self-care, morbidity, and mortality. Research has shown that collaborative care (CC) may be a cost-effective treatment. However, its cost-effectiveness in this patient group has not yet been established. Therefore, the aim of this study was to evaluate the cost-utility of CC for the treatment of comorbid MDD in chronically ill patients in the outpatient general hospital setting. The study was conducted from a health care and societal perspective.

Methods: In this randomized controlled trial, 81 patients with moderate-to-severe MDD were included; 42 were randomly assigned to the CC group and 39 to the care as usual (CAU) group. We applied the TiC-P, short-form Health-Related Quality of Life questionnaire, and EuroQol EQ-5D 3 level version, measuring the use of health care, informal care, and household work, respectively, at baseline and at 3, 6, 9, and 12 months follow-up.

Results: The mean annual direct medical costs in the CC group were €6,718 (95% confidence interval [CI]: 3,541 to 10,680) compared to €4,582 (95% CI: 2,782 to 6,740) in the CAU group. The average quality-adjusted life years (QALYs) gained were 0.07 higher in the CC group, indicating that CC is more costly but also more effective than CAU. From a societal perspective, the incremental cost-effectiveness ratio was €24,690/QALY.

5.1 INTRODUCTION

Major depressive disorder (MDD) is deemed to become the leading cause of disability in 2030 [115] and is a risk factor for a chronic physical condition[116]. The prevalence of comorbid MDD in chronic physical conditions, such as chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), and congestive heart failure (CHF), is estimated to be between 7% and 16% [117]. However, comorbid MDD often goes unrecognized in such cases as it may be difficult to distinguish these symptoms from the symptoms of the underlying medical condition [118].

Comorbid MDD in chronic physical conditions is associated with maladaptive behavior, such as noncompliance with medical treatment recommendations. This is tripled in MDD,[119] with deterioration of general functioning, lower quality of life, and higher costs over the short and long terms [120]. For example, DM patients with comorbid MDD report symptoms more frequently than DM patients with a similar severity of their chronic condition but without comorbid MDD, and this leads to increased medical testing and therefore higher costs [121]. In the case of DM and CHF, patients with comorbid MDD suffer greater health losses [116,119] and have up to twofold higher medical costs compared to DM or CHF patients without comorbid MDD [122].

It has been suggested that disease management interventions [123] aimed at the treatment of MDD in patients with a chronic physical condition might increase the quality of life and decrease costs. In such programs, patients play an active role in their treatment and a care manager coordinates the treatment in collaboration with other medical specialists. A specific form of disease management is collaborative care (CC), which has been proven to be effective in the USA, the UK, and the Netherlands [116,124-128]. The findings of an efficacy study [25,129] showed that when CC was applied in the outpatient general hospital setting for chronic medically ill patients with comorbid MDD, there was no additional effect on the likelihood of remission and response compared to care as usual (CAU). However, it did significantly reduce the number of adverse medical events, which in turn may affect the quality of life. Since then, several systematic reviews have been undertaken exploring the effect of CC related to several chronic physical

conditions, establishing its effect in terms of depressive symptoms over CAU. This has been found for cancer [130], coronary heart disease [131], and DM[132-134].
The efficacy of the model as a generic approach applicable for a variety of chronic physical conditions and in the case of multimorbidity has also been explored in systematic reviews. A meta-analysis of individual participant data found CC to be effective against MDD in chronic physical conditions [135], and a systematic review found that CC is not only effective in reducing depressive symptoms, but also physical symptoms in chronic physical conditions with comorbid MDD [136].

In terms of cost-effectiveness studies on CC for MDD, a review was published in 2010[32] showing that CC overall was more expensive, but increased the quality of life, with an incremental utility of between 0.03 and 0.12 quality-adjusted life years (QALYs). The studies in this review were mostly conducted in the USA and performed in a primary care setting. Another systematic review on studies in primary care found a dominance of CC over CAU[137]. Since then, a randomized controlled trial (RCT) that explored the cost-effectiveness of CC for MDD in primary care established its dominance over CAU [26,111,138]. Another study in the occupational health setting found that CC did reduce costs, but also the effects in that setting[24,80,80,139]. Only one study has investigated the cost-effectiveness of CC for patients with a chronic medical illness with comorbid MDD, namely DM. This study showed that CC was associated with a low increment in medical health care costs, while gaining high benefits[140].
There is ongoing debate from the health services perspective concerning which setting is most fitting for CC of patients with comorbid MDD in chronic physical conditions: the primary care setting or the general hospital setting[141]. Cost-effectiveness may be one of the aspects taken into account in such a debate. However, so far, no cost-effectiveness studies regarding CC have been performed in the general hospital setting. This study aims to do so from a health care and a societal perspective.
The primary objective of this article is to assess the cost-utility of CC for the treatment of comorbid MDD in chronic medically ill patients in the outpatient general hospital setting from a societal perspective, taking all relevant costs and effects into account.

5.2 METHODS

Design

A multicenter RCT was conducted from September 2007 to October 2010 in outpatient clinics for DM, COPD, inflammatory bowel disease (IBD), and chronic heart failure (CHF) in five general hospitals in the Netherlands in Amsterdam, Almelo, Hengelo, Ede, and Maastricht. The study consisted of a two-armed randomized controlled trial, with randomization at the patient level. Patients in the participating departments who screened positive on the patient health questionnaire-9 (PHQ-9)[112] and had an MDD according to the mini international neuropsychiatric interview (MINI)[79] were randomly allocated to the intervention group or the CAU group within their outpatient clinic by a blinded research assistant, using a computerized method to avoid assignment bias. The patients were not blinded for their group allocation. This method of randomization is often followed in psychiatric intervention research[142]. The intervention group received CC from a consultant psychiatric nurse (CPN), and in some cases antidepressant medication from the consultation–liaison (CL) psychiatrist in the department of Consultation–Liaison Psychiatry of the participating hospitals. The control group received CAU. The study protocol was approved by the Medical Ethics Committee (METC) of the VU University Medical Center and is described in greater detail elsewhere[129].

Study oversight

This RCT was part of the Depression Initiative, a national initiative to improve depression management in the Netherlands[23,27,81]. A steering group, consisting of the principal investigator (CFC), and senior investigators involved in the design, management, and analysis of the trial (ATFB, LHR), monitored the progress in quarterly meetings to oversee the project.

Participants

During the inclusion period, all patients who had visited the participating outpatient departments in the previous year and had a confirmed chronic physical condition as specified in their medical records were selected from the medical files and were invited to participate by the nurses receiving them for their regular outpatient visits. The nurses handed them an envelope containing an information letter, an informed consent form, and the screening questionnaire (depression

subscale of the PHQ-9) with a return envelope. Patients who consented and screened positive for depression then received the baseline questionnaire by mail. Patients who met the inclusion criteria based on the patient files but did not visit the participating departments received the same package by mail. In the information letter, the patients were asked if they were willing to participate in a study investigating mental problems and treatment options in the general hospital setting. If they agreed to participate, they were asked to sign the informed consent form and return it together with the completed questionnaire to the researchers, who then contacted them to arrange to conduct the MINI[79].
Inclusion criteria were the presence of a chronic physical condition, informed consent, age >18 years, and having a comorbid MDD as defined by a score of ≥10 on the PHQ-9[112] and a positive MINI[79].-Exclusion criteria were insufficient knowledge of the Dutch language, dementia or delirium, alcohol or drug addiction as a main diagnosis, psychotic or bipolar disorder, suicidality, and pregnancy.

Intervention

In CC, treatment was provided by a team consisting of the patient, the CPN care manager, and the CL psychiatrist at the outpatient clinic of the general hospital according to an algorithm and monitored by a web-based tracking system that functioned as a supportive decision aid for the CPN care manager. Supervision and consultation by the CL psychiatrist was provided when the CPN care manager experienced difficulties in this process. The CC treatment encompassed guided self-help and problem-solving treatment (PST) provided by the CPN care manager in a one-to one session, antidepressants prescribed by the CL psychiatrist according to an algorithm, and consultations with the CL psychiatrist if necessary. According to the stepped care principle, treatment response was monitored biweekly with the PHQ-9. More details of the intervention are described elsewhere.[15,16]

Care as usual

The control group patients received usual care in the general hospital setting, which consisted of a medical specialist monitoring their medical illness and advising the patient to seek treatment for their depressive symptoms from a primary care physician if they felt the need[25,129].

Measures

Data collection was performed by the Trimbos Institute in cooperation with the participating hospitals. After providing informed consent, patients received assessment questionnaires by mail at baseline (T0), and after 3 months (T1), 6 months (T2), 9 months (T3), and 12 months (T4).

Quality of life

Quality of life was assessed with the EuroQol EQ-5D 3 level version (EQ-5D-3L)[10,13]. This generic health index is a standardized, validated instrument that encompasses five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension consists of three levels: no problems, some problems, and extreme problems. Therefore, it defines a total of 243 different health states. The mean utility scores were estimated by applying the area-under-the-curve (AUC) method, implemented by summing the areas of the geometrical shapes obtained by linearly interpolating between utility scores over the study period[11]. Dutch tariffs were used to estimate utilities.

Health care utilization costs

Part 1 of the treatment inventory cost in psychiatric patients (TiC-P)[13] is a validated instrument that measures direct medical costs by estimating the number of contacts with health care services during the previous 3 months. We calculated the costs by multiplying the amount of care by the corresponding reference unit prices from 2016 (indexed to unit prices from 2014)[86]. The direct costs estimated by the TiC-P were as follows: costs for the general practitioner (GP), mental health care institute, psychiatrist/psychologist at an outpatient center or hospital, occupational health care, medical specialist, paramedic care provider, social worker, consultation for alcohol/drugs, alternative treatment, self-help care, admission to part-time day care, (psychiatric) hospital admission, and medication. These costs were taken into account as they are part of the validated instrument. The CPN was the care manager in the CC group and was therefore important for our analysis. The unit price estimation was based on gross wages per year, working hours, session length of 1 hour, preparation of written reports, overheads, bonuses, and training. The amount of care provided by the CPN was recorded using a separate question about resource use. The indirect costs considered were household and informal costs. The inclusion of productivity costs related to paid work is especially relevant when the intervention is targeted at patients of working

age. Due to the high age of the study population, we could reasonably expect cost-effectiveness outcomes to be unaffected by productivity costs, and therefore they could be ignored even when adopting a societal perspective[143]. However, the costs of household work and informal care are considered highly relevant in this study population. We therefore included these costs outside health care.
In general, travel distances in the Netherlands are small, and consequently the costs are low. To avoid further increasing the numbers of questions asked of the patients, travel costs were not considered.

Indirect costs
The second part of the TiC-P contains the short-form Health-Related Quality of Life (SF-HLQ)[14]. This part assesses the amount of informal care and household work.

Cost-utility
An incremental cost-effectiveness ratio (ICER) was calculated to obtain the costs per QALY, dividing the incremental costs by the incremental effects.

Statistical analyses
Analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 19.0, R (version 3.0.3.6), and Excel (2010). First, the direct costs and quality-of-life scores were calculated in SPSS. The cost-effectiveness analysis was performed from a health care and a societal perspective. Uncertainty in the analysis was assessed using bootstrapping in R, with 5,000 iterations. Bootstrapping was conducted by drawing samples from the original sample (with replacement). For each of the bootstrapped samples, a generalized estimating equation model was applied for each outcome variable (ie, quality of life or costs). Costs were adjusted for the number of chronic conditions and age. Quality of life was adjusted for quality of life at baseline and age. We used a multilevel model (generalized estimating equation) to adjust for imbalances between treatment arms and to allow for the correlation between measurements over time. By using this model, we could easily allow for correlation between measurements over time. We used a log link function with a gamma distribution for the costs and an identity function with a Gaussian distribution for quality of life. A correlation matrix with an autocorrelation structure was used for both costs and effects. In this way, 5,000 predicted incremental costs and 5,000 predicted incremental QALYs were generated. Each of the 5,000 ICERs was calculated as the mean of the

predicted incremental costs divided by the mean of the incremental QALYs, expressed on a cost-effectiveness plane and a cost-acceptability curve [144]. For this analysis, an “intention-to-treat” approach was used.
According to the Council for Public and Health Care (RVZ)[145], the threshold in relation to the acceptability of the treatment depends on the severity of disease and uncertainty in the ICER, with a maximum of €80,000/QALY, and this is the decision rule that we applied in this study.

5.3 RESULTS

Population

A total of 11,330 patients were approached by mail or at the desk. Of these, 43% consented to screening. Reasons for lack of consent were inability to locate the patients because of a change of address, language problems, and among the persons approached at the desk, self-reported fatigue due to their chronic physical condition, which hampered collaboration. After the MINI and checking for exclusion criteria, 81 patients with moderate-to-severe MDD could be randomized. Forty-two of these patients were randomly allocated to the CC group and 39 to the CAU group. Fig. 5.1 provides a flowchart of the participants over the course of the study. Table 5.1 summarizes the baseline demographic and clinical characteristics for these patients. There were no significant differences in sociodemographic or clinical characteristics between the CC and CAU groups.

Fig 5.1| Flowchart participants

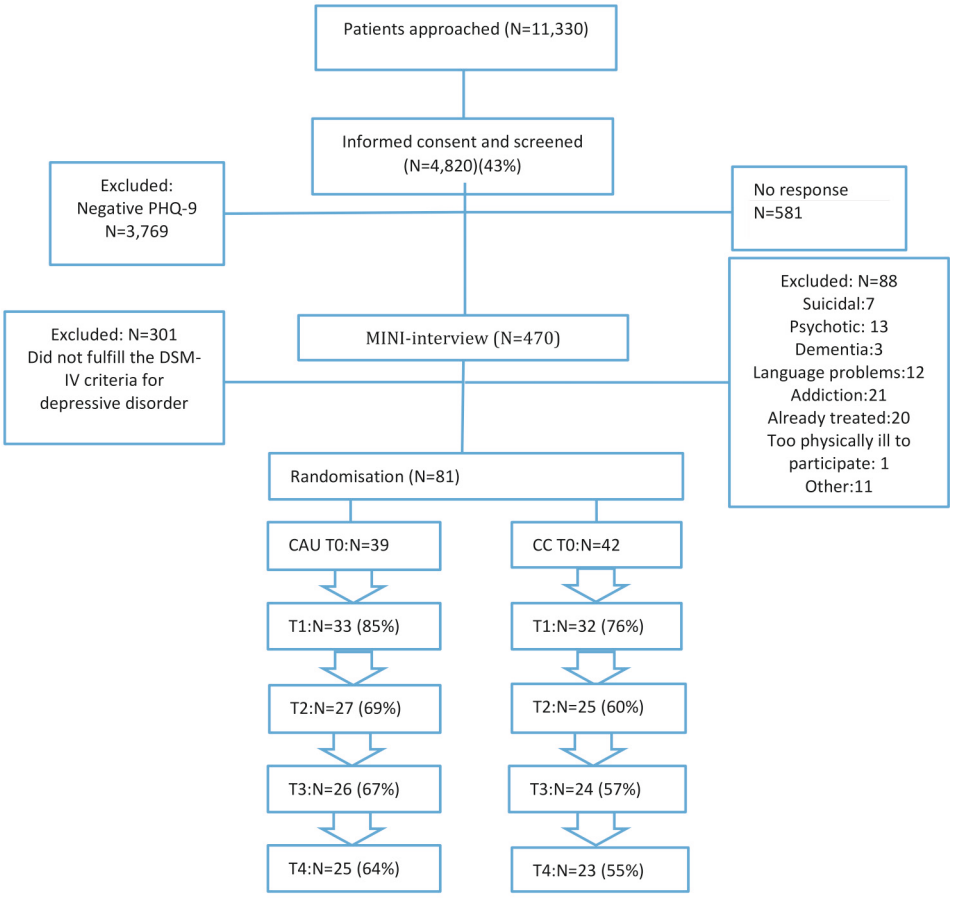


Table 5.1| Baseline characteristics of the participants

Group	Collaborative care (N=42)	Care as Usual (N=39)	p-value
Male sex (%)	52.4	70.0	0.525
Age, mean (SD)	57 (11.6)	60 (11.6)	0.239
Dutch nationality (%)	95.2	90.0	0.522
Married or living with partner (%)	54.8	50.0	0.960
Education beyond high school (%)	26.2	30.0	0.945
Number of chronic medical conditions, mean (SD)	4.2 (2.4)	4.4 (2.4)	0.747
Severity of medical symptoms, LKV-checklist, mean (SD)	1.1 (0.4)	1.0 (0.5)	0.143
Paid job (%)	33.3	23.8	0.460
PHQ-9 score, mean (SD)	16.6 (4.7)	16.5 (4.0)	0.974
Diabetes Mellitus	40.5	35.9	0.415
Chronic Obstructive Pulmonary Disease	23.8	35.9	
Irritable Bowel Syndrom;	0	2.6	
Congestive Heart Failure	35.7	25.6	

Explanation of acronyms: LKV= Physical symptom checklist [Lichamelijke Klachten Vragenlijst; PHQ-9=Patient Health Questionnaire

Dealing with missingness

Our analysis used a multilevel model. In this way, the skewness of the data, baseline corrections, and correlation between measurements over time could be taken into account. The advantage of a multilevel model (a generalized estimating equation model) is that the data are implicitly imputed by the model and the predictions of the model. The pattern of missingness in the data on quality of life and costs is shown in Table 5.2. Decisions on the variables in the model were made

by plotting the residuals of the models and by using the quasi-likelihood under the independence model criterion (QIC).

Table 5.2| Missing values in quality of life and cost data (N=81)

	Percentage of complete data: Quality of life (EQ-5D-3L)[40-41]	Percentage of complete data: Costs (TIC-P)[42]
T0	100%	96.3%
T1	72.8%	80.2%
T2	64.2%	61.7%
T3	61.7%	59.3%
T4	59.3%	55.6%

Quality of life

The utility scores for quality of life were calculated per measurement moment, as shown in Table 5.3. The mean utility scores at baseline were low in both the groups: 0.43 (standard deviation [SD] =0.31) in the CC group and 0.45 (SD =0.28) in the CAU group. The CC group improved significantly over time. In the CAU group, the utility values gained were 0.01 (95% confidence interval [CI]: –0.04 to 0.05) and in the CC group 0.07 (95% CI: 0.02 to 0.13). The difference in effect was not significant over time: 0.07 (95% CI: –0.003 to 0.14).

Table 5.3| Mean utility scores [40-41]

	Collaborative care (n=42)	Care as usual (n=39)
T0	0.43 (0.31)	0.45 (0.28)
T1	0.57 (0.30)	0.44 (0.28)
T2	0.51 (0.33)	0.50 (0.31)
T3	0.58 (0.32)	0.49 (0.30)
T4	0.54 (0.33)	0.50 (0.30)

Direct medical costs

The direct medical costs calculated per health care provider are shown in Table 5.4. The costs of the CPN (the care manager in the CC group) amounted to €291 in the CC group. The costs for the psychiatrist/psychologist were respectively €159 and €187 in the CC and CAU groups.

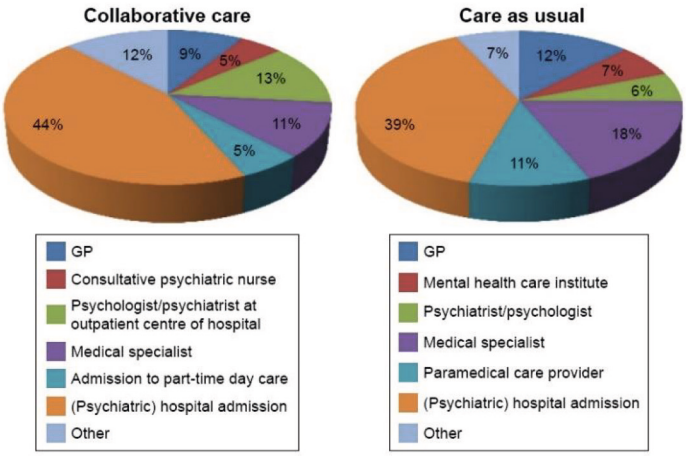
Table 5.4| Unit costs, average number of contacts per patient, measured by the TIC-p and costs by health care providers per year (Euro's 2016)

	Collaborative care (n=42)					Care as usual (n=39)			
	Unit costs (€)	Costs, mean (SD)	Number of visits, mean (SD)	% of patients	missings[1]	Costs, mean (SD)	Number of visits, mean (SD)	% of patients	Missings[1]
General Practitioner (GP)	€67	€507 (520)	7.6 (7.8)	81	11	€383 (399)	5.8 (6.0)	83	3
Consultative psychiatric nurse	€82	€291 (262)	3.5 (3.2)	80	0	€0 (0)		0	0
Mental Health Care Institute	€113	€110 (335)	1.0 (3.0)	19	11	€211(687)	1.9 (1.0)	25	3
Psychiatrist/ psychologist	€95	€159 (333)	1.7 (3.5)	35	11	€187 (363)	2.0 (3.8)	31	3
Psychologist/ Psychiatrist at outpatient centre or hospital	€143-€289	€735 (1011)	3.9 (5.1)	61	11	€67 (171)	0.4 (1.0)	20	3
Occupational healthcare	€33	€11 (43)	0.3 (1.3)	0[1]	11	€14 (43)	0.4 (1.3)	11	4
Medical specialist	€92	€649 (588)	3.8 (2.9)	97	11	€572 (544)	4.4 (3.7)	92	4
Paramedical care provider	€33	€214 (288)	6,5 (8,8)	55	11	€336 (721)	10,3 (22)	39	3
Social worker	€66	€147 (580)	1.9 (7.9)	0	11	€40 (106)	0.6 (1.8)	19	3
Consultation alcohol/drugs	€31	€5 (20)	0.0 (0.2)	0[2]	11	€0 (0)	0.2 (0.6)	0[2]	4
Alternative treatment	€51	€5 (20)	0,1 (0,4)	0[2]	11	€27 (109)	0.5 (2,1)	0[2]	3
Self help care	€58	€2 (11)	0.0 (0.2)	0[2]	11	€0 (0)	0.0 (0.0)	0[2]	3
Admission to parttime Daycare	€172-€281	€314 (1644)	1.7 (9.0)	0[2]	11	€19 (115)	0.1 (0.7)	0[2]	3
(Psychiatric) Hospital admission	€305-€648	€2556 (9150)	5.4 (17.7)	26	11	€1195 (3051)	2.3 (5.6)	31	3
Antidepressant medication		€51 (97)	-	100	11	€50 (100)	-	97	3

[1]To provide a better overview, we imputed the costs per health care provider with zero when over time there was a missing (but not all measurements were missing). For the model, costs were not imputed. [2] Values were rounded and therefore when less than 0.5% of the patients used a service, this number was rounded to 0

The percentage of patients who contacted the medical specialist or had a psychiatrist/psychologist consultation at an outpatient clinic was higher in the CC group compared to the CAU group. After applying the model and bootstrapping the data, the average costs per patient for the CC group were €6,490 (95% CI: 3,290 to 10,645) and the average costs per patient for the CAU group were €4,801 (95% CI: 2,878 to 7,149), resulting in a difference of €1,689 (95% CI: –2,006 to 5,974). The main costs are presented in the pie chart shown in Fig. 5.2.

Fig 5.2| Pie charts presenting the percentage of costs of health care providers for the CC (left) and CAU(right groups.



Indirect costs

As shown in Table 5.5, the indirect costs for informal care and household work were, respectively, €189 (407) and €302 (474) for the CC group. For the CAU group, these costs were €213 (399) and €155 (306).

Table 5.5.| Costs per hour, number of hours, total costs, and number of missings for informal care and household work (Euro's 2016)

		Collaborative care (n=42)			Care as usual (n=39)		
	Costs per hour	Number of hours (SD)	Costs	Number of missings	Number of hours (SD)	Costs	Number of missings
Informal care	€14	13 (29)	€189 (407)	12	15 (28)	€213 (399)	6
Household	€23	13 (20)	€302 (474)	15	7 (13)	€155 (306)	12

Health care perspective

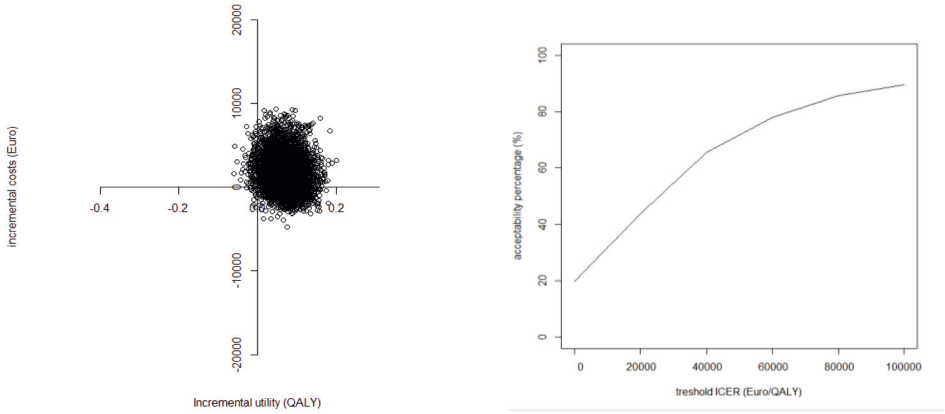
The combination of higher direct medical costs and higher effects resulted in an ICER of €28,366/QALY, as shown in Table 5.6.

Table 5.6.| Incremental costs and effects from health care and a societal perspective

	Collaborative Care (n=42)	Care As Usual (n=39)
Health care perspective		
Average direct medical costs (€)	6,522 (CI 95%; 3,239 to 10,760)	4,582 (CI 95%; 2,782 to 6,740)
Average utilities (QALY)	0.07 (CI 95%; 0.02 to 0.13)	0.01 (CI 95%; -0.04 to 0.05)
Incremental costs (€)	1,939 (-1,751 to 6,428)	
Incremental utility	0.07 (CI 95% -0.002 to 0.14)	
ICER (Euro/QALY)	28,366	
Societal perspective		
Average indirect costs	6,718 (CI 95%; 3,541; 10,680)	5,038 (CI 95%; 3,159 to 7346)
Average utilities (QALY)	0.07 (0.02 to 0.13)	0.01 (-0.04 to 0.05)
Incremental costs (€)	1680 (-1,951 to 5,911)	
Incremental utility	0.07 (CI 95% -0.002 to 0.14)	
ICER (Euro/QALY)	24,690	

In Fig. 5.3, the cost-effectiveness plane and the cost-acceptability curve are shown. As can be seen, 80% of the ICERs fall into the north-east quadrant, indicating a combination of higher effectiveness and higher direct medical costs for the CC group, and 17% of the ratios fall into the south-east quadrant, indicating that CC generates greater utilities and is less expensive compared to CAU.

Fig 5.3| cost-effectiveness plane (left) and cost-acceptability curve (right) from a healthcare perspective



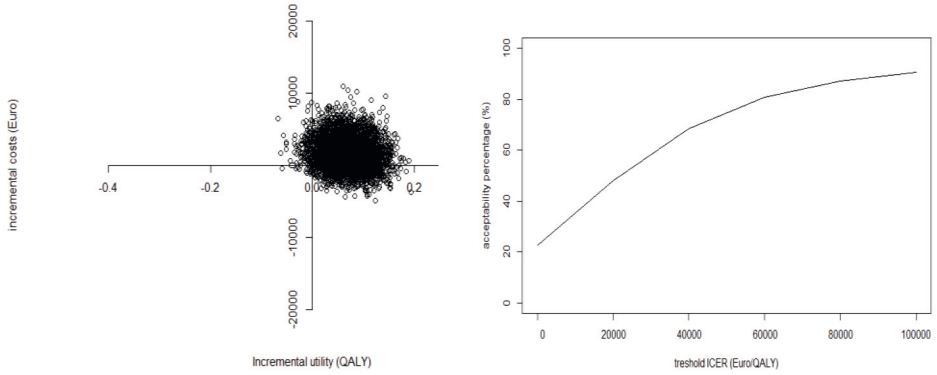
At a threshold of €20,000/QALY, there is 40% probability that the intervention is accepted. At an ICER of €60,000/QALY, there is 80% probability that the intervention is accepted.

Societal perspective

Again, there was a combination of higher direct medical costs and higher effect in the CC group, which resulted in an ICER of 24,690/QALY, as shown in Table 5.6. Although the indirect costs estimated were higher in the CC group, the model predicted otherwise, namely that the costs should actually be lower.

After bootstrapping, the ICERs were again plotted on a cost-effectiveness plane and a cost-acceptability curve (Fig. 5.4). In this case, 77% of the ICERs fall into the north-east quadrant of the cost-effectiveness plane, indicating that CC is associated with higher costs and also higher effects compared to CAU and 20% fall in the south-east quadrant, indicating higher costs and lower effects.

Fig 5.4| cost-effectiveness plane (left) and cost-acceptability curve (right) from a societal perspective

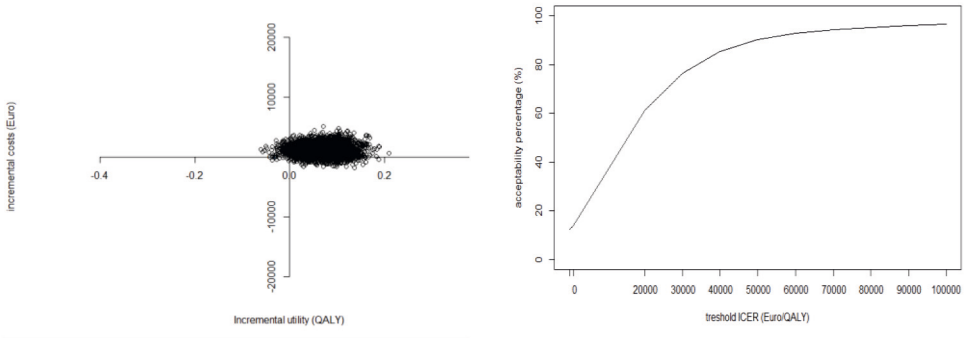


At a threshold of €20,000/QALY, there is 60% probability that the intervention is accepted. At an ICER of €60,000, there is 80% probability that the intervention is accepted.

Sensitivity analysis

A sensitivity analysis was performed from a societal perspective on admission to psychiatric hospital. These costs were relatively high in the CC group, but the number of contacts was relatively low. The costs for the CC group were now €4,287 (95% CI: 2,945 to 5,923) and the costs for the CAU group were €3,155 (95% CI: 2,378 to 4,034). The difference in costs was €1,132 (95% CI: −521 to 2,939). There was only a change in the incremental costs per QALY to €18,732/QALY. In addition, the majority of the cost–effect ratios (88%) still fall into the north-east quadrant and 10% into the south-east quadrant. The cost-effectiveness plane and the cost-acceptability curve are plotted in Fig. 5.5.

Fig 5.5| Sensitivity analysis; cost-effectiveness plane (left) and cost-acceptability curve (right) from a societal perspective



5.4 DISCUSSION

This study is the first cost-utility study of CC for the treatment of comorbid MDD in patients with a chronic physical condition, namely DM, COPD, IBD, or CHF, in a general hospital outpatient setting. The higher costs and higher effects in the CC group lead to an ICER of €24,690/QALY from a societal perspective. We apply a decision rule of a maximum of €80,000/QALY, as explained earlier. The acceptability curve shows that at €20,000/QALY, there is a relatively low probability that the intervention is accepted. However, at a threshold of €60,000/QALY, the probability of acceptance increases to almost 80%. In this case, the ICER is €24,690/QALY, which, in view of the significant disease burden of the patients, may be acceptable. When a health care perspective was considered, the ICER decreased to €18,732/QALY. A sensitivity analysis was conducted to investigate the effect of the costs of admission to a psychiatric hospital as these costs were relatively high, but the number of patients using them was relatively low. After the sensitivity analysis, the ICER decreased and CC became more effective. The sensitivity analysis showed that the results are robust. This is a better outcome than the study on CC in MDD in the occupational health setting, which found CC to be less costly but also less effective than CAU[139]. It is also a better outcome than the study on CC in MDD in primary care, which found that, taking a health care perspective, CC was less cost-effective due to higher costs compared to CAU, which led to an ICER of €53,717/QALY. Hence, in terms of cost-effectiveness, CC may be particularly promising in patients with chronic physical conditions with comorbid MDD who receive treatment in the outpatient general hospital setting. According to the Council for Public and Health Care (RVZ), the threshold in relation to the acceptability of treatment depends on the severity of disease and uncertainty in the ICER, with a maximum of €80,000/QALY[145]. According to this decision rule, an innovative CC model based on the psychiatric consultation services of general hospitals may be a cost-effective intervention. However, replications of this research are necessary.

In both the groups, the largest part of the costs was due to hospital admissions for patients' chronic physical conditions, which indicates the high disease burden in this patient group. Admission costs in the CC group were higher compared to the CAU group. However, these costs were due to a relatively small group of patients, indicated by the large SD. Apart from that, the direct medical costs in the CC group

were mainly caused by visits to a psychiatrist/psychologist at an outpatient center or hospital, the CPN care manager, and admission to part-time day care. This study was conducted from a societal perspective; however, the productivity costs were negligible as the age of the patients was high, and they were consequently in general no longer part of the working population. Furthermore, we did not have data on the utilization of emergency care and therefore we could not estimate these costs. The same holds for medication for physical comorbid conditions. However, we do not expect these costs to be different between the two interventions. Hence, they are not expected to affect the ICER. With respect to occupational health care, we expect these costs not to be relevant due to the high age of the study population, meaning that they will generally be retired.
Over time, the quality of life improved in both groups, but the quality of life in the CC group increased more (significantly). In the effect study[25], there was no significant difference between the two groups in terms of total remission or of treatment response regarding depressive symptoms, as measured by the PHQ-9[112]. However, the number of adverse events did significantly differ between the groups, decreasing more in the CC group, and this may subsequently have contributed to improved quality of life despite the continued presence of depressive symptoms. Further research is needed to explore the association between adverse effects, hospital admissions, and costs and quality of life in this patient group. The initial quality of life was low in both the CC and CAU groups, indicating that MDD in combination with a chronic disorder greatly affects quality of life. This finding corroborates the review of Simon[140], namely that additional impairment is experienced when depressive patients have a comorbid chronic physical condition. This study seems to show a weak trend toward increased quality of life in the CC group, contrary to the CAU group. However, the average quality of life is still remarkably low for both groups.

As CC was associated with higher costs and higher utilities, the results of this study agree with the findings of the review conducted by van Steenbergen-Weijenburg et al[32]. The improvement in quality of life in CC was also substantiated in our study. Simon et al[32] showed that after 1 year, medical costs for CC in patients with comorbid MDD in DM started to decline and at the end of the second year were lower than in CAU. This positive effect also extended to the benefits of intervention. This indicates that higher cost-effectiveness may be attained if a

longer follow-up period is conducted, and this should be a topic for further research.

Research is warranted exploring how to lower the relatively high costs found to be associated with CC for this patient group with a high disease burden. New developments, such as E-health and M-health interventions, have been suggested as alternatives for face-to-face psychotherapeutic treatments in this patient group; however, the expectations in terms of cost-effectiveness have as yet remained unfulfilled. Standalone E-health and M-health interventions in multimorbidity have been found to be associated with patient disengagement and physician withdrawal, and with low effectiveness[146]. Research attempts to develop cost-effective interventions for patients with multimorbidity should focus on patient safety[147], as a study of a tele-monitoring intervention to prevent hospitalization and emergency room visits provided evidence of higher mortality compared to CAU in elderly patients with multimorbidity[148]. The outcomes of our study, showing somewhat more hospital admissions in the CC group, might be related to better monitoring of adverse somatic developments in the CC intervention requiring admission, thus resulting in better quality of life. Hence, also in terms of safety, in this patient group with chronic physical conditions, CC may be the model of choice despite the higher costs. However, this should be explored in further research. Further research might also evaluate a combination of CC and E-health, or tele-monitoring in so-called blended E-health models, in which clinical diagnostic and treatment evaluation is strongly embedded. Thus, no physician withdrawal or patient disengagement should occur. Such treatment should focus not only on the treatment of MDD, but also on better management and quality of life regarding the chronic physical condition at hand, and should also take mortality as an outcome into account[149].

Limitations of the study

The first limitation of this study was the small sample size. Based on the prevalence rates indicated in the literature, this study was originally set up as a clinical trial in one hospital, but due to low inclusion rates, it was extended to a multicenter trial, thus providing sufficient participants to perform the study. Although initially response to the mail invitation was 43%, low inclusion rates were caused by patients having lower comorbid MDD rates than initially expected based on the literature; as can be seen from the flowchart, the actual number of patients

fulfilling the MINI classification for MDD was only 169, of whom a further 88 had to be excluded because of acute suicidality, psychosis, addiction, and dementia, inter alia. This warrants further research into the prevalence of comorbid MDD in chronic physical conditions in clinical cohort studies. Another reason for the low inclusion rates was that patients felt too ill to participate in the study, particularly as their chronic physical condition necessitated focusing on that alone. A further limitation of the study was the high dropout rate, which was to be expected given the high burden of illness due to the combination of psychological and physical complaints in this patient group. This illustrates one of the reasons why few studies have yet been performed in this setting and with this population.

Conclusion

This first study has demonstrated the cost-utility of CC compared to CAU in an outpatient general hospital setting using a relatively long perspective. Despite the small patient group, it was possible to establish some clear findings on the quality of life and costs among outpatients with chronic physical conditions and comorbid MDD. According to the Council for Public and Health Care (RVZ), the threshold in relation to the acceptability of treatment depends on the severity of disease and uncertainty in the ICER, with a maximum of €80,000/QALY. According to this decision rule, an innovative CC model based on the psychiatric consultation services of general hospitals may be a cost-effective intervention. However, replications of this research are necessary.5

This study showed incremental quality-of-life gains in applying a CC model for this patient group. Nevertheless, the low utility scores emphasize the need for further research to improve the (cost-) effectiveness of CC in this highly prevalent and costly group of patients.

6 COST UTILITY ANALYSIS OF A COLLABORATIVE STEPPED CARE INTERVENTION FOR PANIC AND GENERALIZED ANXIETY DISORDERS IN PRIMARY CARE

Based on: Goorden M., Muntingh A.D.T. , van Marwijk H.W.J., Spinhoven P., Adèr, H.J., van Balkom A.J.L.M., van der Feltz-Cornelis C.M., Hakkaart-van Roijen L. (2015). Cost utility analysis of a collaborative stepped care intervention for panic and generalized anxiety disorders in primary care. Journal of Psychomatic Research, 77(1):57-63.

Abstract

Objective: Generalized anxiety and panic disorders are a burden on the society because they are costly and have a significant adverse effect on quality of life. The aim of this study was to evaluate the cost-utility of a collaborative stepped care intervention for panic disorder and generalized anxiety disorder in primary care compared to care as usual from a societal perspective.

Methods: The design of the study was a two armed cluster randomized controlled trial. In total 43 primary care practices in the Netherlands participated in the study. Eventually, 180 patients were included (114 collaborative stepped care, 66 care as usual). Baseline measures and follow-up measures (3, 6, 9 and 12 months) were assessed using questionnaires. We applied the TiC-P, the SF-HQL and the EQ-5D respectively measuring health care utilization, production losses and health related quality of life.

Results: The average annual direct medical costs in the collaborative stepped care group were 1854 Euro (95% C.I., 1726 to 1986) compared to €1503 (95% C.I., 1374 to 1664) in the care as usual group. The average quality of life years (QALYs) gained was 0.05 higher in the collaborative stepped care group, leading to an incremental cost effectiveness ratio (ICER) of 6965 Euro per QALY. Inclusion of the productivity costs, consequently reflecting the full societal costs, decreased the ratio even more.

Conclusion: The study showed that collaborative stepped care was a cost effective intervention for panic disorder and generalized anxiety disorder and was even dominant when a societal perspective was taken.

6.1 INTRODUCTION

Generalized anxiety disorder (GAD) and panic disorder (PD) occur in 4% to 8% of patients in primary care [150-153]. They are associated with an adverse effect on quality of life [154-157], higher health care use, reduced productivity and higher health care costs compared to non-anxious individuals [156-158].

Although they are a great burden to the society, anxiety disorders are not specifically recognized and treated by general practitioners (GPs) [151,159-161]. Whereas pharmacological treatment is frequently initiated for generalized anxiety and panic disorders [159,162] research indicates that compared to care as usual, cognitive behavioral therapy is more cost-effective [163], preferred by most patients [164-166] and leads to more sustainable effects [163,167]. Furthermore, continuity of care is not ensured, because response to treatment is rarely monitored. Consequently, there is no opportunity to adapt accordingly [168,169] or intervene post-treatment when considered necessary [151,152]. Continuity of care is, however, important because anxiety disorders often run a chronic or intermittent course [151,152].

To address these problems, collaborative care models have been developed [76]. In collaborative stepped care pharmacological treatment is only indicated if cognitive behavioral therapy is insufficient. In addition, collaborative stepped care may work in a more efficient way in terms of resource use and costs, because of the focus on low intensity treatment in the first steps [76].

There is evidence that the collaborative care model is an effective intervention for patients with anxiety disorders [170-172]. Recently, a study on the effectiveness of collaborative stepped care showed that it is more effective in reducing anxiety symptoms in panic and generalized anxiety disorders than care as usual [28]. Until now there have been no studies on the cost-effectiveness of the collaborative stepped care model for anxiety disorders. Some research has been done regarding collaborative care; however, most of this research has focussed on the cost-effectiveness of treating major depressive disorder which suggested that collaborative care is a cost-effective intervention [173] and is associated with good economic value [31]. Research of Joesch et al. [174] showed that a collaborative care intervention for patients with panic disorder, generalized anxiety disorders, social anxiety disorders and posttraumatic stress disorder provided higher benefits and

only slightly increased costs, compared to usual care. Two previous studies concerning panic disorders indicate that collaborative care is cost-effective [175] or even dominant [176] compared to usual care. However, these studies were conducted in the United States. As significant differences exist between the health systems of the United States and the European countries, results may not be easily generalized to the European health care setting. Furthermore, none of the studies used a stepped component in collaborative care. Finally, most of these studies did not take a societal perspective.

Hence, the aim of this study was to evaluate the cost-utility of a collaborative stepped care intervention compared to a care as usual intervention in patients with panic disorder and generalized anxiety disorder in the primary care setting from a societal perspective.

6.2 METHODS

Recruitment and randomization

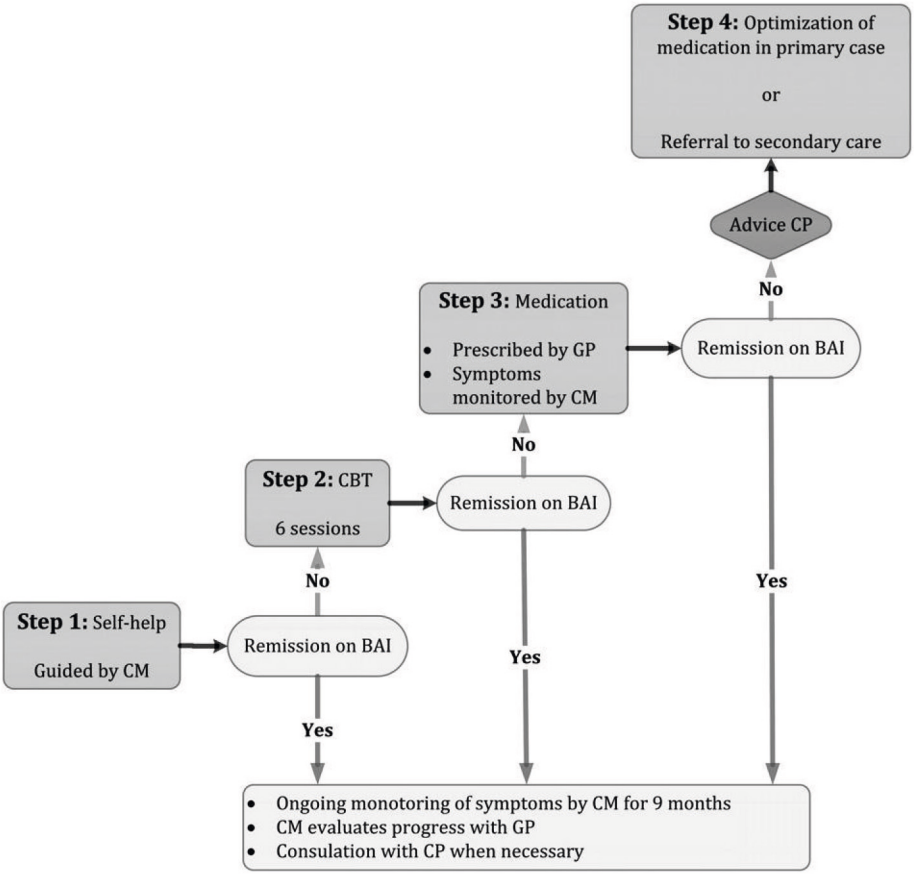
This cost-utility analysis was part of a two armed cluster randomized trial to evaluate the effectiveness of the collaborative stepped care program. Study methods are described in detail elsewhere and are summarized in this section [177]. The study was conducted at 43 primary care practices (PCPs) with 66 GPs in the region of a large mental health center (Rivierduinen) in the Netherlands. The PCPs assigned 31 mental health professionals, consisting of 3 psychologists and 28 psychiatric nurses. Six experienced psychiatrists working in the mental health care center operated as consultant psychiatrists for the intervention group. Cluster randomization was executed at the level of the mental health professionals who were randomized to collaborative stepped care or care as usual. A first selection of patients was performed by the GPs or by a research assistant using the electronic medical records (EMR) of patients. After receiving informed consent and approval from the patients, they were assessed by the Patient Health Questionnaire (PHQ) anxiety subscales [112]. The PHQ is a self-report screening scale which can be used as a self-screening and diagnostic tool for mental health disorders. The patients were then approached for a telephone interview to detect mental disorders (MINI PLUS International Neuro-psychiatric interview) [79]. The MINI PLUS is a short interview which can be used to make diagnoses according to the DSM-IV. This study has been approved by the medical ethics committee [177].

Intervention

The intervention consisted of four integrated evidence-based treatment steps (Fig. 6.1): Guided self-help [36,37], cognitive behavioral therapy, antidepressants according to a medication algorithm and optimization of medication in primary care or referral to secondary care. After each step remission was determined with the Beck Anxiety Inventory (BAI) [178]. If a patient did not achieve the criteria for remission (50% reduction in score and BAI ≤11) after a certain step in the program the patient moved to the next step, otherwise the patient started a relapse prevention program. Mental health professionals (care managers) and general practitioners randomized to the collaborative stepped care group were trained in the intervention. Patient adherence was encouraged by psycho-education, by goal setting and by frequent follow-up appointments in which both adherence and progress were evaluated. If a patient achieved remission after step one, two or

three, relapse prevention was offered by the care manager by calling the patient every month and assessing anxiety symptoms with the BAI. Details of the program are reported elsewhere [177].

Fig 6.1| Collaborative stepped care treatment algorithm



Care as usual

The patients treated by general practitioners assigned to the care as usual condition could obtain any services normally available in the Netherlands. Every PCP could use the assistance of a psychiatric nurse. As the care as usual group was operating as a control group, the general practitioners and psychiatric nurses did not receive additional training. The Dutch guideline of the treatment of anxiety disorders in primary care was accessible for all the GPs [179]. Although GPs were

notified of the diagnosis of referred patients, they were not notified of the diagnosis and participation of screened patients. Patients in the control group were all advised to seek treatment. After one year, type of treatment delivered was assessed at the PCP by a research assistant using a checklist.

Data collection and outcome measures

The data was collected at 3-month intervals: Measurement took place at baseline (T0), three (T1), six (T2), nine (T9) and twelve (T4) months after inclusion. The self-report questionnaires were processed by blinded research assistants.

The aim of this economic evaluation was to assess the cost utility of collaborative stepped care compared to care as usual. All relevant costs to society associated with the burden of anxiety disorders were taken into account: costs attributable to contact with health providers, costs of medications (direct medical costs) and costs of productivity losses due to the anxiety disorder (productivity costs). Cost-utility was calculated by relating the difference in direct medical costs per patient receiving collaborative stepped care or care as usual to the difference in terms of quality adjusted life years gained (cost-utility). This yielded a cost per QALY estimate. Subsequently, productivity costs were also included into the analyses.

Outcome measures

Medical costs

For calculating the total direct medical costs, the Trimbos/IMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P) [85] was used. The TiC-P measures utilization of medical treatment such as the number of contacts with the GP and multiple other care providers (e.g. medical specialists and physiotherapists) during the last three months, as well as the medication used. The costs were estimated using the Dutch guidelines for cost calculations in health care [180]. Reference unit prices from 2009 of the corresponding health care services were applied [86]. Unit costs per contact of the care manager were comparable to those of a nurse practitioner.

Productivity costs

For calculating productivity losses the Health and Labor questionnaire (SF-HQL) [43] was used. The SF-HLQ consists of three modules: absence from work, reduced efficiency at work and difficulties with job performance. Productivity losses as

measured by the Short Form- Health and Labour (SF-HLQ) were valued over 4 weeks by using the "friction cost method" [14]. This method takes into account the economic circumstances that limit the productivity lost to society.

Quality of life

The EuroQol (EQ-5D) [10] generic health index is a standardized, patient-completed instrument which consists of five dimensions (i.e. mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is rated by the patient on three levels (no problems, some problems, and extreme problems). Thus, 243 distinct health states are defined, each with a unique utility score, ranging from 1 (perfect health) to 0 ('death'). The health descriptions were linked to empirical valuations of the Dutch general public, allowing utilities to be computed.

Statistics

Analyses were conducted using Statistical Package for the Social Sciences 19.0 (SPSS 19.0), Statistics and data (Stata 8.0 se) and Excel. First, the direct costs and quality of life scores were calculated by SPSS. No selective dropout was observed [28]. The percentage of non-responders was 15.6% after 3 months, 26.7% after 9 months and 25, 6% after 12 months for the EQ5D. For the direct costs the missingness was the same for the first three time points, but after 12 months it was 25%.

To account for the skewness in the dataset predictive mean matching was used. This method imputes missing values by means of a donor from the nearest neighbor with a distance based on the expected values of the missing variables given the observed covariates. Missing values in direct costs and utility scores per time unit were modeled and imputed with this model. 10 imputed datasets were created. Different baseline variables, like age and gender were included to get a better estimate. To obtain one utility score, the patients' mean utility scores were first linearly interpolated between utility scores over the study period. To calculate utility gain or loss the area-under-the curve method (AUC) was applied [11] and scores were corrected for baseline differences. This method consists of linearly interpolating between the different health states at the different time points. Subsequently the area under the curve is calculated.

Propensity scores were used to correct for baseline differences between both groups. As our outcomes were different from the effect-study of Muntingh and colleagues [28], different confounders were used to balance our scores and propensity scores were again calculated. Confounders used in our study were age, gender, EQ-5D and PHQ score on baseline. The uncertainty in the analysis was assessed using bootstrapping in Excel, with 10,000 iterations. This was expressed in a cost-effectiveness acceptability curve. The acceptability curve illustrates the probability that the cost-effectiveness ratio will be accepted for different cost limits. This information is acquired from a cost-effectiveness plane. In a cost-effectiveness plane, both incremental costs and incremental effects are plotted to account for combinations. These combinations fall into different parts of the plane. If they for instance fall into the north east quadrant, it means that collaborative care generates more effects but also higher costs. If the costs and effects fall into the south east quadrant it means that it is less costly and gains more utilities. This intervention is then called dominant. The percentage of the points falling into the different quadrants is given. It is however not drawn as it contains the same information as the acceptability curve.

An incremental cost-effectiveness ratio was calculated to calculate the costs per quality adjusted life year (QALY). The incremental cost-effectiveness ratio was calculated by dividing the incremental costs by the incremental effects, by the following formula (6.1). All costs from the TiC-P were included to estimate the ICER from a health care perspective.
Productivity costs were also included when the ratio was calculated from a societal perspective.

$$\frac{<Costs_{cc}> - <Costs_{cau}>}{<Effect_{cc}> - <Effect_{cau}>} \qquad (6.1)$$

$< Costs_{cc} >$ = Mean costs per patient in collaborative stepped care
$< Costs_{cau} >$ = Mean costs per patient in care as usual
$< Effect_{cc} >$ = Mean effect per patient in collaborative stepped care
$< Effect_{cau} >$ = Mean effect per patient in care as usual

6.3 RESULTS

Table 6.1 summarizes the baseline demographic and clinical patient characteristics for care as usual and collaborative stepped care. In total 180 participants were included in the study (66 participants in the CAU group and 114 in the CSC group). At baseline, there was a significant difference between the groups on the BAI scores which affected QALYs gained, so propensity scores were calculated to compensate.

Table 6.1| Baseline demographic and clinical patient characteristics for care as usual and collaborated stepped care (collaborative stepped care)

	Collaborative stepped care (N=114)	Care as usual (N=66)	Total (N=180)
Mean age (SD)	44.98 (15.06)	49.08 (15.93)	46.48 (15.47)
Gender (% male)	31 (27.2%)	26 (39.4%)	57 (31.7%)
Number of people with a paid job (%)	77 (67.5%)	41 (62.1%)	118 (65.6%)
Mean BAI score (SD)	24.59 (11.52)	20.04 (11.28)	22.09 (11.55)
Depression score (PHQ9), mean (SD)	9.40 (5.62)	8.98 (5.77)	9.25 (5.66)
EQ-5D, mean (SD)	0.61 (0.25)	0.65 (0.23)	0.64 (0.25)
Level of education			
Elementary school	10 (8.8%)	4 (6.2%)	14 (7.8%)
High school	68 (59.6%)	35 (53.8%)	103 (57.5%)
College	36 (31.6%)	26 (40.0%)	62 (34.6%)
Primary diagnosis			
PD	48 (42.1%)	29 (43.9%)	77 (42.8%)
GAD	32 (28.1%)	17 (25.8%)	49 (27.2%)
PD & GAD	34 (29.8%)	20 (30.3%)	54 (30.0%)
Co-morbid depression			
Yes	34(29.8%)	22(33.3%)	56 (31.1%)
No	80 (70.2%)	44 (66.7%)	124 (68.9%)

Direct medical costs

The total average direct medical costs were €1854 (95% C.I., 1726 to 1986) for the collaborative care group, compared to over €1503 (95% C.I., 1374 to 1664) for the care as usual group. The average number of contacts and costs per health care

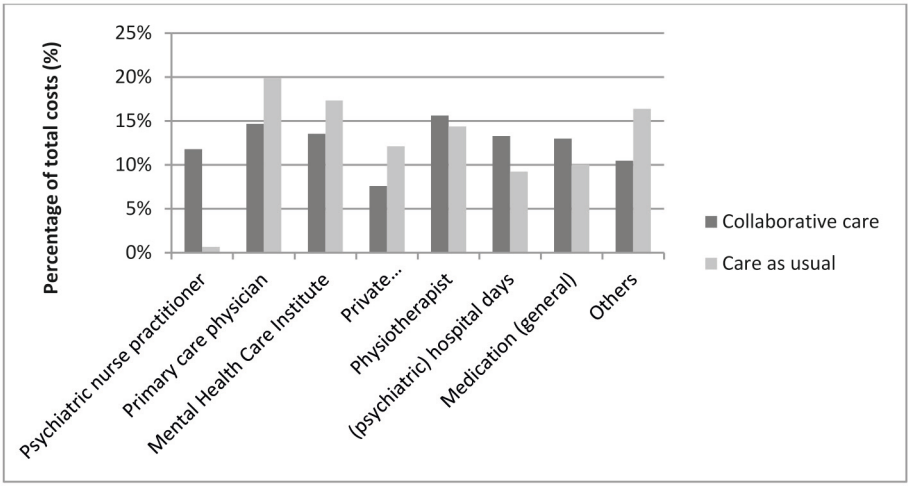
provider are expressed in Table 6.2 and a summary of the largest percentages was plotted in a histogram (Fig. 6.2).

Table 6.2| Average number of contacts and costs by health care providers from baseline to 12 months (Euro's, 2009)

	Collaborative stepped care *				**Care as usual ***			
	Mean costs (SD)	Percentage of total costs	Mean number of contacts (SD)	% patients	Mean costs	Percentage of total costs	Mean number of contacts (SD)	% patients
Psychiatric nurse practitioner	177 (208)	11.8	2.3 (2.7)	50.0	9 (38)	0.7	0.1 (4.9)	6.1
Primary care physician	220 (209)	14.7	3.9 (3.7)	77.2	269 (246)	19.9	4.8 (4.4)	84.8
Mental health care institute	203 (681)	13.5	1.2 (4.0)	14.9	235 (712)	17.3	1.4 (4.2)	13.6
Private psychologist/psy-chiatrist	114 (345)	7.6	1.3 (3.9)	16.7	164 (397)	12.1	1.9 (4.5)	25.8
Psychologist/psy-chiatrist at outpatient center of hospital	6 (36)	0.4	0.0 (0.2)	2.6	17 (100)	1.3	0.1 (0.6)	3.0
Occupational physician	20 (54)	1.3	0.4 (0.9)	15.8	29 (81)	2.1	0.5 (1.4)	15.2
Medical specialist	56 (139)	3.7	1.3 (2.6)	36.8	51 (135)	3.8	1.7 (3.9)	40.9
Paramedic	234 (482)	15.6	6.5 (13.4)	41.2	195 (349)	14.4	5.4 (9.7)	43.9
Social worker	15 (104)	1.0	0.2 (1.6)	2.6	26 (115)	1.9	0.4 (1.8)	7.6
Counseling center for drugs alcohol	0 (0)	0.0	0.0 (0.0)	0.0	0 (0)	0.0	0.0 (0.0)	0.0
Alternative medicine	56 (160)	3.7	1.0 (2.9)	16.7	39 (91)	2.9	0.7 (1.7)	16.7
Selfhelp group	4 (24)	0.3	0.07 (0.5)	2.6	0 (0)	0.0	0.0 (0.0)	0.0
(Parttime) day care	0 (0)	0.0	0.0 (0.0)	0.0	60 (461)	4.4	0.4 (3.0)	1.5
(Psychiatric) hospital days	199 (1022)	13.3	0.4 (2.1)	6.1	125 (492)	9.2	0.3 (1.1)	7.6
Medication (general)	195 (832)	13.0	–	63.2	136 (199)	10.0	–	69.7

* The sum of the mean costs of health care providers is not equal to the average total costs. This is because multiple imputation was performed on the costs after calculating the total costs

Fig 6.2| Overview of the proportion of costs (%) by health care providers plotted in a histogram.



Productivity costs

The indirect costs after imputation were €1052 (SD=2585) and €2007 (SD=1044) respectively for the collaborative care group and the care as usual group. Productivity cost due to absence from work was respectively €586 (SD=1901) and €1423 (SD= 1099) for the collaborative care group and the care as usual group. Costs caused by inefficiency at work were €611 (SD=1552) and €677 (SD=1330) for the collaborative care group and the care as usual group. The sum of the costs is not equal to the total productivity costs as imputation was only performed on the total costs.

Quality of life

Quality of life scores are shown in Table 6.3. The improvement over time in terms of quality adjusted life years (effect) was 0.06 for the care as usual group (95% C.I., 0.04 to 0.07) and 0.11 for the collaborative care group (95% C.I., 0.10 to 0.13). The difference in improvement between both groups was 0.05 and was also significant over time (95% C.I., 0.04 to 0.07).

Table 6.3| Mean utility scores (SD) by treatment arm at baseline, after 3 months, after 6 months, after 9 months and after 1 year

	Collaborative stepped care (n=114)	Care as usual (n=66)
Baseline	0.62 (SD=0.24)	0.60 (SD=0.25)
After 3 months	0.71 (SD=0.22)	0.65 (SD=0.23)
After 6 months	0.73 (SD=0.24)	0.64 (SD=0.26)
After 9 months	0.73 (SD=0.24)	0.72 (SD=0.25)
After 1 year	0.80 (SD=0.19)	0.73 (SD=0.29)

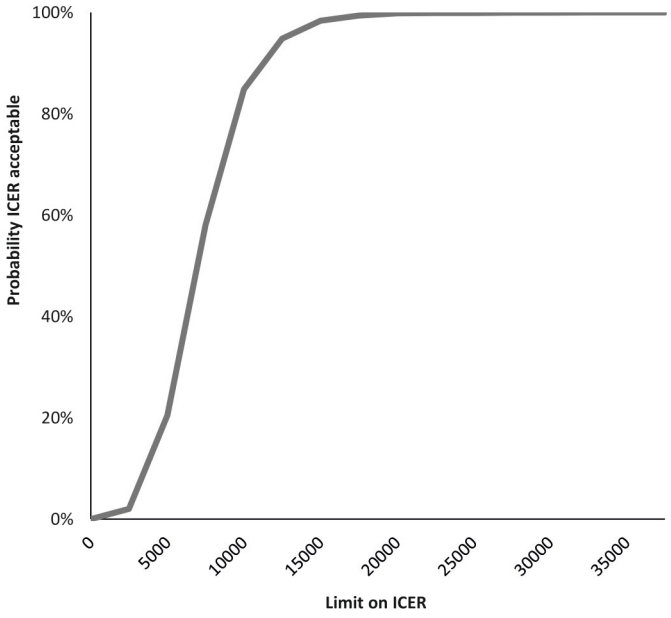
Cost utility analysis (CUA)

The average quality of life years (QALYs) gained was higher in the collaborative stepped care group. The direct medical costs were also higher in the collaborative stepped care group, leading to an incremental cost effectiveness ratio (ICER) of 6965 Euro per QALY.

We first explored the incremental cost utility for the direct costs. The incremental cost-effect ratio (100%) falls in the northeast quadrant of the incremental cost-effectiveness plane, demonstrating that collaborative stepped care is more costly but also more effective than care as usual. Another way to present the uncertainty in the data is the acceptability curve in Fig. 6.3. Bootstrapping the incremental costs and effects resulted in 10,000 associated ICERS. To determine the acceptability of the treatments, we calculated the proportion of ICERS that were below a certain threshold. The threshold is the willingness of society to pay and was varied as it is uncertain. The thresholds and the proportion of ICERS were subsequently plotted in the cost acceptability curve, see Fig. 6.3. The figure shows that, for example, at a threshold of 10,000 Euro/QALY the probability that the ratio is acceptable is more than 90%.

Including productivity costs did change our result as collaborative stepped care became dominant, meaning that it was less costly and more effective compared to care as usual. The ratio decreased to −4977 Euro/QALY. The majority (91%) of the incremental cost-effect ratio now fell into the southeast quadrant demonstrating that collaborative care was dominant. At a threshold of 10,000 Euro/QALY the probability that the ratio is acceptable is 100%.

Fig 6.3. The data in the form of an acceptability curve excluding the productivity costs are presented.



6.4 DISCUSSION

This study is the first cost-utility analysis comparing collaborative stepped care to care as usual for anxiety disorders and shows that collaborative care is a highly cost-effective intervention. This study showed that the cost per QALY was 6,965 Euro/QALY. Including productivity costs decreased the ratio to −4977 Euro/QALY.

According to the Council for Public and Health Care (RVZ) the threshold of the ICER in relation to the acceptability of the treatment has to depend on the severity of disease with a maximum Incremental Cost Effectiveness Ratio (ICER) of 80,000 Euro/QALY. In our study, the uncertainty in the ICER was very low; at a threshold of 20,000 Euro/ QALY the probability that the ICER would be accepted was almost 90% and even 100% when including productivity costs. Hence, treating patients with general anxiety or panic disorder at the general practice applying collaborative stepped care is a highly cost effective intervention.

The differences in medical costs are mainly due to the higher costs of the care manager in the collaborative care group compared to the care as usual group. Physiotherapist costs were high for both groups showing that besides mental health care, somatic care is frequently used [181]. Medical costs of collaborative stepped care were comparable to those of guideline concordant care for patients with anxiety or depressive disorder [109]. Including the productivity costs did change our results as the costs for absence at work were higher in the care as usual group. This finding supports the research of Krol et al. and Smit et al.[5,18], as productivity costs had a considerable effect on our outcomes.

Over time, the quality of life improved more in the collaborative care group when compared to the care as usual group (not significant). In the care as usual group quality of life did not increase much after 9 months, indicating that collaborative stepped care may have a more prolonged effect on the quality of life. In addition, the quality of life improved more rapidly in the intervention group. This may be due to the effectiveness of guided self-help that was administered in the first step of the treatment.

This study produced results which corroborate the findings of Katon et al. [175]and Joesch et al. [174], showing that the costs and effects of collaborative care were

higher compared to care as usual for panic disorder. However, the findings of the current study do not fully support the previous research of Katon et al. [182] which showed that compared to care as usual collaborative care was dominant. Only when including productivity costs, collaborative care became dominant. However, the intervention applied differed from our collaborative care intervention; the psychiatric intervention that was used by Katon et al. [182] consisted of approximately 2 sessions per patient which was less than the approximately 6 sessions per patient in our intervention. In addition, Katon's study [182] did not involve a care manager, who was responsible for the largest part of the additional costs in our study. None of the cost-effectiveness studies [174,175] used a stepped component in collaborative care. All studies were North American and since there are important differences between European and North American health care systems, these studies cannot be generalized without consideration.

In the article of Bower and Gilbody [76], it was suggested that collaborative stepped care may cost less because of lower resource use. However, in the present study resource use of both groups were comparable over time. At baseline, also patients who already received some (≤2 sessions per month) psychological or psychiatric treatment were included, so patients from the care as usual group and collaborative care were already equal in terms of resource use of these mental health care services. Despite the lack of difference concerning resource use, collaborative care was still cost-effective, due to the substantial influence that treatment had on quality of life.

The study was conducted in a naturalized setting, which involved GPs selecting the patients. There was a selection bias for two reasons. Firstly the GPs in the care as usual group had a preference for the collaborative care group and they had difficulties selecting patients for the care as usual group. Secondly the GPs in the collaborative stepped care intervention received training, which might have contributed to their improved ability to detect suitable patients. To minimize selection bias after this initial selection, all patients followed the same procedure with a diagnostic interview conducted by a researcher who was blind for randomization status. After selection patients were obliged to accept the assigned treatment. However, there were still more patients in the collaborative care group (N=114) than in the care as usual group (N=66). This study used cluster randomization, which was necessary because otherwise the usual care would have

been more restricted as the GP would not have had the opportunity to send patients to a psychiatric nurse or psychologist because this professional was trained in the new intervention. In this way, the usual care would have been restricted to prescribe medication or referral to secondary care.

Based on age, gender, PHQ-score, EQ5D-score, level of education, primary diagnosis and comorbidity, the care as usual and the collaborative stepped care group were comparable to patients in primary care. They were not comparable with respect to their BAI score, so propensity scores were used to correct.

Although collaborative stepped care was cost-effective compared to care as usual, the results of this study leave room for improvement [28] . Most importantly, not all the elements of stepped care approach were sufficiently implemented [28]. There was a relatively large proportion of patients (41%) in the collaborative stepped care group who did not want to continue treatment after step 1 [28]. An explanation for this high rate in step 1 is that patients felt that they were sufficiently empowered to cope with their anxiety problems, although they did not achieve criteria for remission. As Scogin et al. [183] already pointed out, research is needed to investigate whether after unsuccessfully being treated, patients with initial lower intensity treatments will be less willing to undergo further, more intensive treatment. Further research is required to explore the reasons. The implementation of collaborative stepped care may be further improved by increasing the case load of care managers, adjusting follow-up procedures to fit into the daily tasks of the care manager and improving medication prescription and adherence by a greater role of the care manager and the psychiatrist in medication management.

Despite some of these limitations, the findings of this study suggest a high cost-effectiveness for collaborative stepped care for anxiety disorders. From a societal perspective, collaborative care becomes even dominant. In combination with the effectiveness study [28], it highly supports the implementation of collaborative stepped care in daily practice and widespread implementation is therefore justified

PART 3: INTERVENTIONS BASED ON COLLABORATION

7 THE COST-EFFECTIVENESS OF FAMILY/FAMILY-BASED THERAPY FOR TREATMENT OF EXTERNALIZING DISORDERS, SUBSTANCE USE DISORDERS AND DELINQUENCY: A SYSTEMATIC REVIEW.

Based on: Goorden M., Schawo S.J., Bouwmans-Frijters C.A., Schee van der E., Hendriks V.M., Hakkaart-van Roijen L. (2016). The cost-effectiveness of family/family-based therapy for treatment of externalizing disorders, substance use disorders and delinquency: a systematic review. BMC Psychiatry, 16: 237

Abstract

Background: Family therapy and family-based treatment has been commonly applied in children and adolescents in mental health care and has been proven to be effective. There is an increased interest in economic evaluations of these, often expensive, interventions. The aim of this systematic review is to summarize and evaluate the evidence on cost-effectiveness of family/family-based therapy for externalizing disorders, substance use disorders and delinquency.

Methods: A systematic literature search was performed in PubMed, Education Resource information Centre (ERIC), PiCarta and Cochrane reviews including studies conducted after 1990 and before the first of August of 2013. Full economic evaluations investigating family/family-based interventions for adolescents between 10-20 years treated for substance use disorders, delinquency or externalizing disorders were included.

Results: 731 articles met the search criteria and 51 studies were initially selected. The final selection resulted in the inclusion of 11 studies. The quality of these studies was assessed. Within the identified studies, there was great variation in the specific type of family/family-based interventions and disorders. According to the outcomes of the checklists, the overall quality of the economic evaluations was low. Results varied by study. Due to the variations in setting, design and outcome it was not feasible to pool results using a meta-analysis.

Conclusions: The quality of the identified economic evaluations of family/family-based therapy for treatment of externalizing disorders, adolescent substance use disorders and delinquency was insufficient to determine the cost-effectiveness. Although commonly applied, family/family-based therapy is costly and more research of higher quality is needed.

7.1 INTRODUCTION

Family therapy and family-based treatment is considered an evidence-based practice treatment for children and adolescents with externalizing disorders, symptoms of delinquency and/or substance use disorder [37,38]. Familial and extra-familial systems are known to influence the individual [184-188], and therefore family/family-based therapy is not only aimed at the individual youth but also at systems surrounding the individual. For instance, delinquency and substance abuse in adolescents have been shown to be influenced by family factors, like parenting style and attachment [184-188]. In addition, a recent review indicated that problems within the extra-familial system, like delinquent peers, problems with bonding at school and in the neighborhood are risk factors for delinquency and problem drinking [188]. As the individual, familial and extrafamilial systems are interconnected, family/family-based therapy not only positively affects the adolescent but also the family (family cohesion) and the extra-familial systems [189].

For the purpose of the present paper, family therapy and family-based treatment is broadly defined as treatments in which primarily family members and/or members of the families' wider networks are involved in the treatment process of resolving problems for young people [190] as opposed to treatments that mainly or solely focus on the individual youth, or treatments that do not focus on youths' problem behavior, like marital therapy.

Well-known forms of family/family-based treatments are Multisystemic therapy (MST) [35], Functional Family Therapy (FFT) [36] and Multidimensional Family therapy (MDFT) [33]. Although there is a large overlap between these types of therapies, there are also some differences [191]. For instance, in FFT and MST there is more focus on antisocial behavior. However, the degree of severity of the disorder is often higher in MST compared to FFT. More details of these differences are described in Appendix 7.1. Recently, Von Sydow et al. [37] systematically reviewed studies on the effectiveness of family/family-based therapy for the treatment of children and adolescents who have externalizing disorders. Their study included disorders like substance abuse, attention deficit hyperactivity disorder, conduct disorder and symptoms of delinquency. They concluded that there is sound evidence that family/family-based therapy is effective with particularly large effect sizes for delinquency and substance abuse measures. However, in the meta

analyses that were included in Von Sydow's systematic review, more cautious conclusions regarding the effectiveness of systemic therapy were drawn. Current health care policy in the Netherlands and elsewhere places emphasis on the provision of effective mental health services in a cost effective way. Family/ family-based interventions are intensive as they consist of a relatively high number of sessions per week and subsequently are relatively expensive [192,193]. Therefore, there is a need for economic evaluations to assess whether additional effects gained through family/family-based therapy in comparison to alternative treatments – if observed – justify the additional costs. Morgan et al. [194] described eight studies, analyzing the cost-effectiveness of family-based treatments for substance abusing adults and adolescents and concluded that some of these treatments could be considered as cost-effective. However, family based therapies like marital therapy, were also included in this study. In addition, the literature search in this study was not systematically conducted and was only considering patients with substance use disorders. To our knowledge, no systematic review of economic evaluations of family/family-based therapy in externalizing, delinquent or substance-abusing adolescents has yet been performed. Hence, this paper presents a systematic review of economic evaluations of systemic interventions in adolescents with externalizing disorders, substance abuse or delinquency.

The aim of the present study was to assess the evidence on cost-effectiveness of family/family-based therapy for adolescents with externalizing disorders, substance use disorders or delinquency, and to evaluate the quality of the existing studies, and the generalizability of the study findings.

7.2 METHODS

The review was performed according to the Cochrane handbook for systematic reviews of interventions [195] and adopted the Preferred Reporting for Systematic reviews and Meta-Analyses (PRISMA) statement [52].

Search strategy

A systematic literature search was performed in Pubmed, ERIC, Psycinfo and Cochrane reviews (including economic trials and clinical trials). These different search engines were used because of their high quality, coverage of large databases and their focus on economic trials. Search terms encompassed the different types of systemic therapy (Functional Family Therapy, Multidimensional Family therapy, Multidimensional Foster Care, Multisystemic Therapy, Family Behavior Therapy and Brief Strategic Therapy) but also more general classifications (systemic therapy, substance abuse treatment, family based therapy, Family based intervention, Family system intervention, Family intervention program). These terms were searched for in title and abstract and were then combined with terms referring to economic evaluations searched for in title and abstract or a Medical Subject Headings (MeSH) term (economic evaluation, cost-effectiveness, cost-utility, cost benefit, cost analysis, cost measure) and in the title (costs). Costs were searched for only in the title, and not in the abstract, because the latter resulted in many irrelevant studies. This search term was included as we noticed that although in some studies both costs and effects were evaluated, the main focus of these studies was to evaluate the costs and a smaller part was referring to the effects. Consequently, when only terms referring to both the costs and effects were included, these studies would have been missed. The search term “Economic modeling” was not explicitly incorporated into the search strategy as the modeling should be part of a cost-effectiveness, cost utility, cost benefit or cost analysis (corresponding with our aim). Abbreviations were also included. To improve our search, MeSH terms were used, see Appendix 7.2 for more details.

Selection strategy

In Fig. 7.1 the selection criteria are described and numbered. The criteria were applied to the studies in chronological order and when a study was excluded based on a criterion the number as shown in Fig. 7.1 was noted. We considered studies from January 1990 until January 2016. The selected study types were clinical/randomized controlled trials (RCT), reviews, systematic reviews and meta-analyses. The treatment needed to consist of a family/family-based intervention, targeted at adolescents (10–20 years old) with a substance use disorder, externalizing disorder or delinquent behavior. The method needed to be a cost or cost- effectiveness/benefit/ utility analysis. When studies were assessed for eligibility based on their abstracts and it was likely that they only contained cost-outcomes and no effect-outcomes, they were also included. To determine the eligibility of the full text articles, the same selection criteria were used, except that accessibility of the study was a requirement (full text available) and studies that only contained costs-outcomes and no effect-outcomes were excluded. The selection of the articles was performed by two researchers independently. Differences in selections were discussed until consensus was reached.

Data extraction and risk of bias

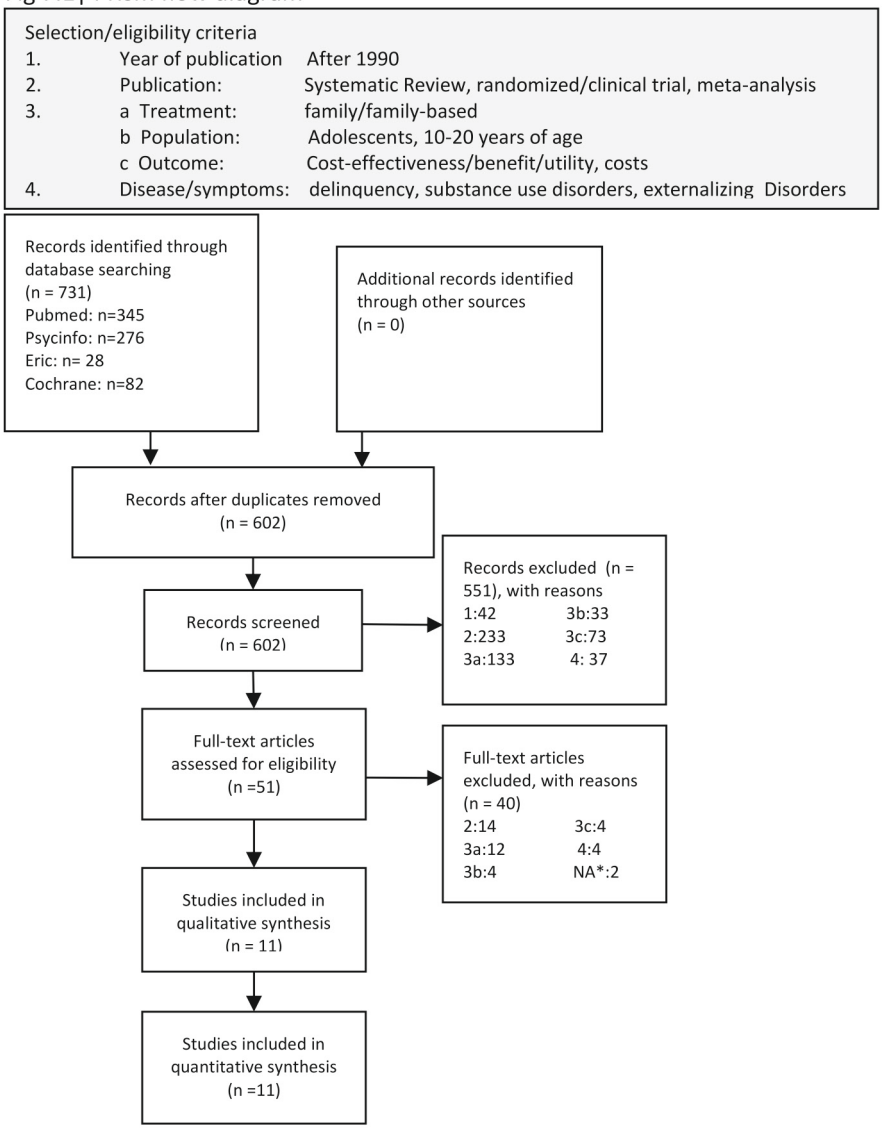
The quality of the studies was assessed with the British Medical Journal Checklist for authors and peer reviewers of economic submissions [196] and the Consensus on Health Economic Criteria (CHEC) list for assessment of methodological quality of economic evaluations [104] as recommended by the Cochrane reviews handbook [195]. We also consulted the critical appraisal of the studies by the NHS Economic Evaluation Database (NHS EED) structured abstract [195]. This is a database from Cochrane library consisting of structured abstracts of economic evaluations of health care interventions. Full economic evaluations were identified from a variety of sources and assessed according to a set of quality criteria. Subsequently, detailed structured abstracts were produced. In addition to the checklists, information about the economic perspective of the study (health care, societal etc.), design, country, follow-up, type of disorder, sample size, study dropout, age, gender, type, duration and intensity of intervention, time horizon, currency and price year, key features of sensitivity analyses and the included cost types were collected for the economic evaluation described in the studies. In accordance with the suggestions in the Cochrane handbook [195] five different biases of the individual studies were addressed: selection bias, performance bias, detection bias, attrition

bias and reporting bias [195]. They were respectively addressed by assessing if patients were properly balanced at baseline, patients and therapists were blinded, outcome assessors were blinded, the amount of dropout in the studies and by reading the protocols of the studies.

7.3 RESULTS

A total of 731 articles met the search criteria. After removal of duplicates and a first selection based on the abstracts, 51 studies matched the inclusion criteria. After assessment for eligibility, 11 studies were selected (see Fig. 7.1).

Fig 7.1| Prism flow diagram



*NA=Not available; Two studies were not available

Characteristics of the studies

An overview of the characteristics of the studies, participants and the interventions is shown in Table 7.1. Ten of the eleven selected studies were published between 2003 and 2015 [197-206] and one study was published in 1996 [207]. Eight of the studies originated from the United States (USA) [197-199,202,204-207]. Remaining studies were initiated in Sweden[201] ,England [203] and Mexico [200]. All studies were (based upon) randomized controlled trials. Two pairs of studies [197,199,202,204]were each based on one sample. Most of the studies compared a family/family-based intervention with care as usual [198,201,203,205-207]. MST was the most researched intervention as it was investigated in eight studies [198,199,201-203,205-207]. In the Study of Borduin et al. [206] Multisystemic Therapy for Problem Sexual Behavior (MST-PSB) was investigated. MST-PSB is an adaptation to MST aimed at the treatment of juvenile sexual offenders. A description of the (non-family/family-based) comparator interventions is shown in Table 7.2. The mean number of sessions of the family/family-based interventions was between 1 and 3 times a week and the mean duration of treatment was between 12 and 31 weeks. The average follow-up time was between 6 and 300 months (25 years); only four studies followed patients for more than 1 year [201,203,205,206]. Two studies were outliers in respect to the time horizon they used (8 years and 25 years)[205,206]. Six studies were aimed at adolescents with substance use disorder [197,202,204,207,208], one study investigated adolescents with a conduct disorder [201], one study adolescents at risk for continuing criminal activity [203],one study adolescents who had experienced a psychiatric crisis [198], another study adolescents who were serious juvenile offenders [205] and one study aimed to investigate juvenile sexual offenders [206]. The average sample size of the 9 studies (with separate samples) was 178 (SD = 163) with a variation between 48 and 600 patients. Follow-up attrition, when registered, was low (not more than 30%). Average age at baseline was 15 (Standard Deviation (SD) = 1) years and between 61 and 96% of the individuals were males. Types of economic analyses included cost-effectiveness analyses [198,200,202,204], cost-benefit analyses [197,201,205,206] and cost offset analyses [203]. The difference between a cost-offset and a cost-benefit analysis is often not well-explained. A cost-offset analysis compares the monetary value of resource use with the monetary value of costs reduced by the intervention (usually health care costs). In contrast to a cost-benefit analysis which also focusses on other outcomes that are translated in monetary outcomes (like translating number of life years gained to a monetary value). In reality, cost-offset analysis is a partial cost-benefit

analysis because it compares the cost of a program with the monetary value of a single outcome (i.e., avoided future health care costs). In two studies, the economic evaluation was not explicitly classified [207,208].

Table 7.1|Features of the studies, participants and the interventions

Study	Features study			Features participants								Features intervention			
	Country	Follow-up (months)	Design	Disorder	Sample Size		Completed study		Age		Sex (% male)		Intervention		Num-ber of ses-sions per week	Treatment, duration (weeks)
					I	C	I	C	I	C	I	C				
Schoenwald et al.,1996 [207]	USA	6 AT	RCT	SUD	59	59	NS		16		79		CAU		2–3[b]	18–19
French et al., 2003 [197]	USA	12a	RCT	SUD			564						Trial 1:			
					102				16		81		MET/CBT5		0–1	6–7
					96				16		86		MET/CBT12		0–1	12–14
					102				16		84		FSN		1–2	12–14
													Trial 2:			
					100				16		79		MET/CBT5		0–1	6–7
					100				16		80		ACRA		1–2	12–14
					100				16		85		MDFT		1–2	12–14
Sheidow et al.,2004 [198]	USA	12 AT	RCT	PC	115		NS		13		67		MST	CAU	NS	16
Dennis et al., 2004 [204]	USA	12	RCT	SUD			564						Trial 1:			
					102				16		81		MET/CBT5		0–1	6–7
					96				16		86		MET/CBT12		0–1	12–14
					102				16		84		FSN		1–2	12–14
													Trial 2:			
					100				16		79		MET/CBT5		0–1	6–7
					100				16		80		ACRA		1–2	12–14
					100				16		85		MDFT		1–2	12–14
McCollister et al.,2009 [199]	USA	12	RCT	SUD	38	42	NS		15	15	84	81	DC	FC	NS[1]	NS[1]
					38				15		84		DC + MST			
					43				15		84		DC + MST + CM			
French et al.,2008 [200]	MEX	7	RCT	SUD	30	30	114		16	16	80	83	FFT	group	NS[1]	NS[1]
					29				16		76		Joint			
					31				16		84		CBT			
Olsson, 2010 [201]	SW	24	RCT	CD	79	77	NS		15		61		MST	CAU	NS	12–20
Sheidow et al.,2012 [202]	USA	12	RCT	SUD	38	42	29	33	15		83		DC	FC	NS[1]	NS[1]
					38		29						DC + MST			
					43		37						DC + MST + CM			
Cary et al., 2013 [203]	ENG	30	RCT	DEL	56	52	46	45	15	15	83	82	MST+ CAU	CAU	3	20
Dopp et al.(2014) [205]	USA	300	RCT	DEL	92	84	70	56	15		69		MST	CAU	3–4	21
Borduin et al.(2015) [206]	USA	107	RCT	DEL	24	24	24	22	14		96		MST-PSB	CAU	3	31

Legend: I =intervention, C=comparator, NS=not stated,NS[1]=reference to non-accessible article, NA=not applicable, USA=United States of America, SW=Sweden, ENG= England, MEX=Mexico,SUD=substance use disorder, CD=conduct disorder, PC=psychiatric crisis, MST=multisystemic therapy, Joint=combination of individual and family therapy, group=skill-focused psycho-education group intervention, IT= individual treatment, MST-PSB=MST for Problem Sexual Behavior, CAU=care as usual, FSN=family support network, MDFT=multidimensional family treatment, MET/CBT12=motivational enhancement treatment/cognitive behavior therapy, 12 sessions;MET/CBT5=motivational

enhancement treatment/cognitive behavior therapy, 5 sessions, ACRA= adolescent community reinforcement approach, DC=drug court with community services, DC +MST=drug court with multisystemic therapy, DC +MST + CM=drug court with mst and enhanced with a contingency management programs,FFT=functional family therapy, FC=family court with community services, [a] Cost data was only collected only during 3–9 months, [b] The intensity of the treatment was between 2 and 3 times a week; AT=after treatment

Table 7.2| Descriptions of comparator interventions

FSN	Cognitive behavioral sessions and motivation treatment in combination with a family component
MET/CBT5	Motivational component and a cognitive behavioral component, to enhance motivation to change drug abuse and to grow the skills to maintain and regulate abstinence
MET/CBT12	MET/CBT5+ 7 sessions of CBT are added to the therapy.
FC	Family court treatment with community services/ Appearance court 2 times a year/ outpatient alcohol and drug abuse service from the local center of the state's substance abuse commission
DC	Drug court treatment with community services/ Appearance court 1 time a week/ outpatient alcohol and drug abuse service from the local center of the state's substance abuse commission and monitoring drug abuse
CM	Frequent in home screens for drug use, voucher system contingent on clean screens, and drug refusal training.
ACRA	Identifying reinforces that are incompatible with the drug use and to strengthen those
CAU	Sheidow et al. [198] admission to a psychiatric unit and aftercare Schoenwald et al. [207] outpatient substance abuse services Olsson et al. [201] Not described Cary at al. [203] Youth Offending Team (YOT) Dopp et al. [205] Individual Therapy (IT) Borduin et al. [206] Cognitive behavioral group therapy and individual services (from local juvenile court)

FSN family support network, MET/CBT5 motivational enhancement treatment/ cognitive behavior therapy, 5 sessions, MET/CBT12 motivational enhancement treatment/cognitive behavior therapy, 12 sessions; ACRA adolescent community reinforcement approach, FC family court with community services, DC drug court with community services, CM contingency management programs, CAU care as usual

Outcomes of the studies

Details of the interventions and outcomes of our analyses are described in Tables 7.3 and 7.4. Costs were indexed until 2014.

Table 7.3| Studies that reported substance use disorder

Studies considering costs and effects of substance abuse				
Dennis (2004)		**Costs intervention and comparators (per episode of care per patient)(MET/CBT 5, MET/CBT 12, FSN, ACRA, MDFT)** In trial 1 MET/CBT 5,MET/CBT 12 and FSN were compared. In trial 2 MET/CBT 5, ACRA and MDFT were compared. Costs were collected with a program (DATCAP) which yields estimates such as the total annual opportunity cost of treatment and the labor cost per client. MET/CBT 5 (trial 1): €1,226 MET/CBT 12 (trial 1): €1,305 FSN (trial 1): €3,576 **Effects intervention and comparators (per patient) (MET/CBT 5, MET/CBT 12, FSN, ACRA, MDFT)** Met CBT 5 (trial 1) Days of abstinence: 269 Recovery*: 28% Met CBT 12 (trial 1) Days of abstinence: 256 Recovery: 17% MET FSN (trial 1) Days of abstinence: 260 Recovery: 22% *Recovery is defined as having no use or abuse dependence problems and living in the community	MET/CBT 5 (trial 2): €1,716 ACRA (trial 2): €1,551 MDFT (trial 2): €2,205 Met CBT 5 (trial 2) Days of abstinence: 251 Recovery: 23% ACRA (trial 2) Days of abstinence: 265 Recovery: 34% MDFT (trial 2) Days of abstinence: 257 Recovery: 19%	**Difference cost** The difference in costs were not showed in this study. However, it was showed that the differences were significant. **Difference effects** The difference in effects were not showed in this study However it was showed that the difference was not significant.
	Results	**Cost per day of abstinence:** Met CBT5 (trial 1): €541 Met CBT 12: €677 Met FSN: €1,667 **Costs per person in recovery** Met CBT5 (trial 1): €4,360 Met CBT 12: €41,172 Met FSN: €16,651		**Cost per days of abstinence:** MET/CBT5 (trial 2): €991 ACRA: €729 MDFT: €1,143 **Costs per person in recovery** MET/CBT5 (trial 2): € 7,337 ACRA: €4,913 MDFT: €12,970
French (2008)		**Costs intervention per patient (FFT, Joint and CBT)** FFT: Treatment costs: €1,817 Joint: treatment costs: €2,847 CBT: Treatment costs: €1.439	**Costs comparator per patient (Group)** Group: Treatment costs: €990	**Difference costs** The difference in costs were not showed in this study

		Effects intervention per patient (FFT, Joint and CBT) FFT: % days marijuana use 4 months: 25.3 %of days marijuana use 7 months:39.8 YSR delinquency score 4 months: 8.2 YSR delinquency score 7 months:9.2 Joint % of days of marijuana use 4 months:38.1 marijuana use 7 months:35.4 YSR delinquency score 4 months: 9.1 YSR delinquency score 7 months:8.5 CBT %of days marijuana use 4 months: 50.6 %of days marijuana use 7 months:51.8 YSR delinquency score 4 months: 10.2 YSR delinquency score 7 months:10.4	**Effects comparator per patient (Group)** Group % of days of marijuana use 4 months: 54.8 marijuana use 7 months:40.7 YSR delinquency score 4 months: 9.5 YSR delinquency score 7 months:9.4	**Difference effects with regression model:** FFT versus group: % days marijuana use 4 months: 20.11* % days marijuana use 7 months: 4.87 YSR delinquency score 4 months: -0.60 YSR delinquency score 7 months: 0.15 CBT versus group % days marijuana use 4 months: 4.76 % days marijuana use after 7 months: 18.27 YSR delinquency score 4 months: 0.38 YSR delinquency score 7 months: 0.42 Joint versus group % days marijuana use after 4 months: -14.86 % days marijuana use after 7 months "-2.00 YSR delinquency score 4 months: -0.50 YSR delinquency score 7 months: -1.50
	Results	Group therapy was most cost-effective, none of the other therapies were significantly different in effect compared to group therapy. So the intervention with the lowest costs was considered to be most cost-effective.		
Shei-dow (2012)		**Costs Intervention (DC, DC+MST, DC+MST+CM)** Treatment costs DC: €9,083 DC+MST: €12,369 DC+MST+CM: €12,859	**Costs comparator (FC)** Treatment costs FC: €3,679	The difference in costs were not shown in this study

	Effects intervention (DC, DC+MST, DC+MST+CM) **DC** Marijuana use (days): -16.65 Polydrug use (days): 1.41 Alcohol use (days): 0.49 Heavy alcohol use (days): 0.86 SRD status offenses (incidents): -7.24 SRD Theft (incidents): -3.28 SRD crimes against persons (incidents): -2.69 DC+MST Marijuana use (days): -30,17 Polydrug use (days): :-1.11 Alcohol use (days): 0.27 Heavy alcohol use (days): -0.45 SRD status offenses (incidents): -11.11 SRD Theft (incidents): -2.79 SRD crimes against persons (incidents): -3.90 DC+MST+CM Marijuana use (days): -27.86 Polydrug use (days): -6.76 Alcohol use (days): -7.56 Heavy alcohol use (days): -4.13 SRD status offenses (incidents): -10.38 SRD Theft (incidents): -3.19 SRD crimes against persons (incidents): -2.4	**Effects comparator (FC)** Marijuana use (days): -15,43 Polydrug use (days): 2.27 Alcohol use (days): 2.97 Heavy alcohol use (days): 0.76 SRD status offenses (incidents): 9.22 SRD Theft (incidents): -5.54 SRD crimes against persons (incidents): 0.49	**Difference effects**: The difference in effects were not showed in this study
Results	ACERS (Average cost-effectiveness ratios) were calculated; average costs/ difference between mean incidents before and after treatment(negative means inefficient)		

	FC	DC	DC+MST	DC+MST+CM
Marijuana use:	€238	€545	€410	€461
Polydrug	(215-262)	(474-617)	(377-442)	(434-488)
use:	€-1,619	€-6,425	€11,209	€1,912
Alcohol	(-8,839-5,601)	(-27,541-14,692)	(-3,757-26,175)	(1,624-2,182)
use:	€-,1,239	€-18,814	€-44,838	€1,699
Heavy alcohol	(-6,546-5,601)	(-42,034-4,405)	(-61,014-28,662)	(1,486-1,912)
use:	€-4,857	€-10,535	€27,592	€3,109
SRD status	(-10,632-918)	(-28,804-7,733)	(-14,636-69,821)	(1,708-4,511)
offenses:	€-400	€1,254	€1,114	€1,239
SRD	(-1,206-398)	(1,132-1,376)	(907-1,321)	(1,009-1,496)
theft:	€663	€2,773	€4,428	€4,032
SRD crimes	(428-899)	(-2.441-7,987)	(-1,224-10,081)	(1,204-6,859)
against persons:	€-7,588	€3,377	€3,175	€5,346
	(-10,667--4,510)	(2,976-3,777)	(236-6,123)	(4,723-5,968)

Studies considering costs and benefits of substance abuse

Schoenwald (1996)	**Costs interventions(MST)** Mental health outpatient (total): €4,242 Mental health day treatment (total): €5,423 Mental health residential treatment (total): €6,899 Psychiatric inpatient (total): €15,752 Psychiatric emergency room (total): €1,150 Substance abuse outpatient (total): €2,001 Substance abuse residential treatment (total): €3,450 Substance abuse inpatient (total): €16,098 Marine Institute day treatment (total): €18,926 Marine Institute residential treatment (total): €3,036 Treatment costs: €266,516	**Costs comparator (CAU)** Mental health outpatient (total): €19,075 Mental health day treatment (total): €1,118 Mental health residential treatment (total): €0 Psychiatric inpatient (total): €18,513 Psychiatric emergency room (total): €3,450 Substance abuse outpatient (total): €20,272 Substance abuse residential treatment (total): €43,695 Substance abuse inpatient (total): €93,771 Marine Institute day treatment (total): €28,618 Marine Institute residential treatment (total): €0	**Benefits interventions** Incarceration days: €65,427	**Benefits CAU** Incarceration days: €120,851
	Costs interventions (MST) Mental health outpatient (total): €4,242 Mental health day treatment (total): €5,423 Mental health residential treatment (total): €6,899 Psychiatric inpatient (total): €15,752 Psychiatric emergency room (total): €1,150 Substance abuse outpatient (total): €2,001 Substance abuse residential treatment (total): €3,450 Substance abuse inpatient (total): €16,098 Marine Institute day treatment (total): €18,926 Marine Institute residential treatment (total): €3,036 Treatment costs: €266,516	**Costs comparator (CAU)** Mental health outpatient (total): €19,075 Mental health day treatment (total): €1,118 Mental health residential treatment (total): €0 Psychiatric inpatient (total): €18,513 Psychiatric emergency room (total): €3,450 Substance abuse outpatient (total): €20,272 Substance abuse residential treatment (total): €43,695 Substance abuse inpatient (total): €93,771 Marine Institute day treatment (total): €28,618 Marine Institute residential treatment (total): €0	**Benefits interventions** Incarceration days: €65,427	**Benefits CAU** Incarceration days: €120,851

Results	MST: Total costs (costs+ benefit) with incarceration=€408,919 and the total costs (costs+benefit) with incarceration per youth=€6,930 CAU: Total costs (costs+benefit) with incarceration=€335,845 and the costs (costs+benefit) per youth=€5,693. Difference in total between groups =€1,019			
French (2003)	**Costs interventions (MET/CBT 5, MET/CBT 12, FSN, ACRA, MDFT)** Treatment costs were measured		**Benefits interventions (MET/CBT 5, MET/CBT 12, FSN, ACRA, MDFT)** **Health service utilization;** Outpatient clinic/doctor's office visit Days bothered by health/medical problem **Substance-absue treatment** utilization; Days in detoxification program; Day in inpatient treatment program; Day in long-term residential program; Intensive outpatient program visits; Regular outpatient program visits **Education and employment;** Days missed at school or training**;** Personal income**;** Days stressful for parents Day missed of work or school by parent **Criminal activity;** Arrests**;** Day on probation**;** Days on parole**;** Days in prison/jail**;** Days in juvenile detention		
	Incremental arm: MET/CBT5:€1,226 MET/CBT12: €1,305 FSN: €3,576	Alternative arm: MET/CBT5: €1,716 ACRA: €1,551 MDFT: €2,216	**Incremental arm:** MET/CBT5 Baseline €2,553 3 months: €2,133 6 months: €1,671 9 months: €945 12 months: €1,217 MET/CBT12 Baseline: €2,179 3 months: €2,433 6 months: €828 9 months: €1,431 12 months: €687 FSN: Baseline: €2,552 3 months: €4,525 6 months: €1,783 9 months: €1,205 12 months: €1,726	**Alternative arm:** MET/CBT5 Baseline €2,694 3 months: €3,587 6 months: €2,213 9 months: €2,275 12 months: €1,907 ACRA Baseline: €2,506 3 months: €3,691 6 months: €1,748 9 months: €3,113 12 months: €3,237 MDFT: Baseline: €2,019 3 months: €3,938 6 months: €1,467 9 months: €2,573 12 months: €2,098
Results	Net economic benefits (benefits+costs) relative to baseline: 3 different models were administred; Model 1: only time dummies for each of the follow-up periods (as treatment conditions were not included, we did not show the results. Model 2: time dummies and indicator variables for treatment condition. Model 3: time and treatment variables withan indicator variable for site. The last specification added numerous demographic and environmental controls. MET/CBT12: Model 2: €-198 (349) Model 3: €-171 (346) Model 4: €-340 (334) FSN: Model 2: €607* (343) Model 3: €653 (340) Model 4: €250 (333) *p<0.1		Acra: Model 2: €369 (436) Model 3: €530 (430) Model 4: €554 (405) MDFT Model 2: -€61 (441) Model 3: €128(436) Model 4: €100 (530)	

MC collister (2009)	**Costs interventions (DC, DC/MST, DC)**	**Costs comparators (FC)**	**Benefits interventions (DC, DC/MST, DC)**	**Benefits comparators (FC)**
	Treatment costs	Treatment costs	Criminal activity costs according to Self-reported criminal activity (SRD):	Self-reported criminal activity (SRD):
	DC: €8,156 DC/MST: €11,547 DC/MST/CM: €11,547	FC: €3,304	DC: €28.601 (94.314) DC/MST: €65.640 (240.559) DC/MST/CM: €80.222 (336.461)	FC: €206.045 (545.581)
Results	After 12 months, total costs relative to FC with multivariate model (intervention costs not incorporated): DC: €-124,877 (-84,107) DC/MST: €-117,918 (-82,570) DC/MST/CM: €140,274 (179,066) * All DC conditions generated reduction in crime costs, greater than average costs of treatment.			

Currency and price year: Sheidow (2004).USD, 1997; Dennis (2004).USD, 1999; French (2008). USD, 1998; Sheidow (2012).USD 2004. When a price year was not stated it was estimated by taking the mean year of the study duration or when not available subtracting 1 from the year of publication of the study. MST=multisystemic therapy; Joint=Combination of individual and family therapy; group=skill-focused psycho-education group intervention; CAU=Care As Usual; FSN= Family support network; MDFT= multidimensional family treatment; MET/CBT12: Motivational enhancement treatment/ cognitive behavior therapy, 12 sessions; MET/CBT5= Motivational enhancement treatment/ cognitive behavior therapy, 5 sessions ;Acra= Adolescent community reinforcement approach; DC=Drug Court with community services; DC+MST=Drug court with Multisystemic therapy; DC+MST+CM=Drug court with MST and enhanced with a contingency management programs; FFT= functional family therapy; FC= Family court with community services

Table 7.4| Studies considering externalizing disorders and delinquency

Studies considering both costs and effects				
Sheidow (2004)	**Costs intervention (MST)** Medicaid (government insurance program)costs (inpatient, Outpatient, Pharmacy, other costs) , Other treatment costs paid for by study MST Medicaid costs: 0-end treatment (4 months): €9,311 (±7,755) Medicaid costs: End treatment-12 months: €13,237 (±15,144) Other treatment costs paid for by study: €11,617	**Costs comparator (CAU)** Medicaid (government insurance program)costs (inpatient, Outpatient, Pharmacy, other costs) , Other treatment costs paid for by study CAU Medicaid costs: 0-end treatment (4 months): €13,255 (±5,762) Medicaid costs: End treatment-12 months: €15,207 (±18,485) Other treatment costs paid for by study: €0	**Difference costs ($Costs_{CAU}$-$Costs_{MST}$) (after risk adjusted model):** 0-end treatment (total costs): End treatment- 12 months post-treatment (total costs):	-€1,828 -€452 (SE=14)
	Effects intervention CBCL: Externalizing scores, internalizing scores: GSI: Global severity index are measures The main effects were not showed in this study but only differences over time were presented.	**Effects comparator** CBCL: Externalizing scores, internalizing scores: GSI: Global severity index The main effects were not showed in this study but only differences over time were presented.	**Difference effects ($Effects_{CAU}$-$Effects_{MST}$) (after risk adjusted model):** 0-end treatment: end treatment- 12 months post-treatment:	Externalizing: -14.75 (SE=8.37) Internalizing: -14.19 (SE=9.26) Global severity index: -0.03 (SE=0.497) Externalizing: 3.29 (SE=9.97) Internalizing :-6.18 (SE=9.67) Global severity index: -0.37 (SE=0.428)
Results	ICER: 1 point improvement in externalizing scores for usual care was associated with a cost of €1,561. 1 point improvement in externalizing scores for MST was associated with a costs of €404. After 12 months both treatments have comparable costs and externalizing scores.			
Studies considering costs and benefits				
Olsson[4] (2010)	**Costs intervention (MST)** Treatment costs: €10.789 Travel: €53 (133)	**Costs comparator (CAU)** Travel: €151 (225)	**Benefits intervention (MST)** Psychosocial and behavioral effects: - Social services (placement): €31,947 (€65,869) Social services (nonplacement): €8,557 (19,459) National board of institutional care (rebate): €3.009(11.014) National board of institutional care (placements): €3.593 (31.937)	**Benefits comparator (CAU)** Program effects: Social services (Placement): €36,707 (73,407) Social services (nonplacement): €14,914 (15,405) National board of institutional care (rebate): €2,375 (9,949) National board of institutional care (placements): 0 (0) SEK Wider societal costs and benefit: set to zero

			Wider societal costs and benefit: set to zero Psychosocial and behavioral effects: set to zero	
Results	The net loss to society after two years is €4,555			
Cary (2013)	**Costs interventions (MST+YOT)** Treatment costs: €3.013 (1.940) Social worker: €733 (446) Reparation worker: €100 (131) Drugs worker: €54 (74) Connexions worker: €33 (69) Parenting worker: €36 (137) Group worker: €17 (34) Psychologist: €17 (67) Other appointments: €20 (59)	**Costs comparator (YOT)** Social worker: €1.023 (779) Reparation worker: €83 (14) Drugs worker: €78 (152) Connexions worker: €18 (61) Parenting worker: €90 (182) Group worker: €22 (44) Psychologist: €30 (91) Other appointments: €26 (95)	**Benefits interventions (MST+YOT)** Offending behavior (Young offender information system): €12,397 (18 472)	**Benefits comparator (YOT)** €15,409 (24,013)
Results	Difference (Costs+benefits) between treatments €1,612 (95% C.I-€7,699-€to 10,924) In the cost-effectiveness plane, we see , there is 63% probability that the net benefit of MST+Yot is positive in favor of the MST+YOT group.			
Dopp (2014)	**Costs interventions (MST)** Costs per patient: €9,756	**Costs comparator (CAU)** Costs per patient: €1,843	**Benefits intervention (MST)** Benefits for taxpayer: Murder: €0 Sexual offenses: €922 Robbery: €188 Assault: €1,156 Property: €2,395 Drug: €916 Theft: €131 Stolen property: €24 Fraud: €259 Assault: €236 Drug: €777 TOTAL: €7,007	**Benefits comparator (IT)** Benefits for taxpayer: Murder: €0 Sexual offenses: €602 Robbery: €308 Assault: €1,697 Property: €1,899 Drug: €1,334 Theft: €188 Stolen property: €53 Fraud: €224 Assault: €294 Drug: €598 TOTAL: €7,197
Results	**Crime victim avoided expenses** Murder/manslaughter: Tangible: €6,125 Intangible: €11,365 Sexual: Tangible: €259 Intangible: €3,439 Robbery: Tangible: €575 Intangible: €1,422 Assault: Tangible: €539 Intangible: €2,926	**Net present values and benefit-cost ratios** <u>Net present values</u> Referred youths: Taxpayer: €2,348 Crime victim tangible: €2,389 Crime victim intangible €9,375 Cumulative: €29,939 Siblings: Taxpayer: €674 Crime victim tangible: €2,702	**Sensitivity analysis** Max (plausible) values Crime victim intangible benefits: €48,087 Sibling juvenile arrest rates: €30.74 Discount rates: €24.063 Min (plausible) values Crime victim intangible benefits: €17.561 Sibling juvenile arrest rates:- Discount rates: €36.704	

	Property: Tangible: €3,914 Intangible: €0 Drug: Tangible: €0 Intangible: €0 TOTAL Tangible: €11,412 Intangible: €19,151	Crime victim intangible: €4,533 Cumulative: €6,561 Sibling pairs: Taxpayer: €1,399 Crime victim tangible: €3,499 Crime victim intangible: €11,238 Cumulative*: €31,962 *: Includes the incremental costs of MST over IT <u>Benefit cost ratio</u> Referred youths Taxpayer: 1.3 Crime victim tangible: 1.3 Crime victim intangible 2.19 Cumulative: 4.78 Siblings: Taxpayer: - Crime victim tangible: - Crime victim intangible: - Cumulative: - Sibling pairs Taxpayer: 1.18 Crime victim tangible: 1.44 Crime victim intangible: 2.42 Cumulative*: 5.04 *: Includes the incremental costs of MST over CAU		
Borduin (2015	Costs interventions (MST-PSB) Costs per patient: €10,566	Costs comparator (CAU) Costs per patient: €4,610	**Benefits intervention (MST-PSB)** Benefits for taxpayer Murder: €0 Sexual offenses: €6,419 Robbery: €2,189 Assault: €0 Property: €2,831 Drug: €1,899 Theft: €180 Stolen property€0 Fraud: €91 Assault: €250 Drug: €512 TOTAL: €14,371	**Benefits comparator (CAU)** Benefits for taxpayer Murder: €0 Sexual offenses: €15,756 Robbery: €0 Assault: €2,194 Property: €3,790 Drug: €518 Theft: €65 Stolen property: €39 Fraud: €75 Assault: €289 Drug: €112 TOTAL: €22,839
Results	**Crime victim avoided expenses** Murder/manslaughter: Tangible: €41,048 Intangible: €76,169 Sexual: Tangible: €1,739 Intangible: €23,044 Robbery: Tangible: €3,850	**Net present values and benefit-cost ratios** <u>Net present values</u> Referred youths: Taxpayer: € 79,891 Crime victim tangible: €70,538 Crime victim intangible €122,397 Cumulative*: €284,739 Siblings:	**Sensitivity analysis** Max (plausible) values: Crime victim intangible benefits: €387,085 Discount rates: €239,009 Posttreatment arrest rates: €478,277 Min (plausible) values: Crime victim intangible benefits: €188,217 Discount rates: €311,107 Posttreatment arrest rates: €91,673	

Intangible: €9,529	Benefit cost ratio
Assault:	Referred youths
Tangible: €3,612	Taxpayer: 14.41
Intangible: €19,611	Crime victim tangible: 12.84
Property:	Crime victim intangible 21.55
Tangible: €26,244	Cumulative: 48.81
Intangible: €0	*: Includes the incremental
TOTAL	costs of MST over CAU
Tangible: €76,494	
Intangible: €128,353	

Currency and price year: Schoenwald (1996).USD, 1996; French (2003). USD, 1999; Mc Collister (2009). USD,2008; Olsson(2010) SEK, 2007; Cary (2013). Pounds, 2008; Dopp (2014) USD, 2012; Borduin(2015) USD,2013.. When a price year was not stated it was estimated by taking the mean year of the study duration or when not available subtracting 1 from the year of publication of the study. For Schoenwald et al. (2006), 1996 was taken as prices year although the study was published in 1996. This was because they already published their first study in 1996 (preliminary findings) and subsequently probablythe current study was conducted in 1996. MST=multisystemic therapy; Joint=Combination of individual and family therapy; group=skill-focused psycho-education group intervention; CAU=Care As Usual; FSN= Family support network; MDFT= multidimensional family treatment; MET/CBT12: Motivational enhancement treatment/ cognitive behavior therapy, 12 sessions; MET/CBT5= Motivational enhancement treatment/ cognitive behavior therapy, 5 sessions ;Acra= Adolescent community reinforcement approach; DC=Drug Court with community services; DC+MST=Drug court with Multisystemic therapy; DC+MST+CM=Drug court with MST and enhanced with a contingency management programs; FFT= functional family therapy; FC= Family court with community service

Substance abuse

Six studies were identified which included adolescents that were treated for substance abuse [197,199,200,202,204,207]. Three of these studies considered costs and effects [25, 27, 29] and three considered both costs and benefits [197,199,207].

-Studies considering costs and effects

In the study of French et al. [200] FFT was shown to be more cost-effective than a skill-focused psycho-education group intervention for treating substance use disorders and delinquency after the first 4 months. After 12 months no such effect was observed. Therefore, after 12 months the cost-effectiveness analysis reduced to a simple cost minimization analysis. As only treatment costs were considered (narrow perspective), the intervention with the lowest intervention costs, in this case group therapy, was considered to be economically beneficial. In another study, Dennis et al. [204] computed cost-effectiveness ratios and these ratios indicated that overall, the most cost-effective interventions were Motivational Enhancement Treatment/ Cognitive Behavior Therapy, 5 sessions (MET/CBT5) and Motivational enhancement treatment/ Cognitive Behavior Therapy, 12 sessions (MET/CBT12) when compared to Family Support Network (FSN) in Trial 1 and Adolescent Community Reinforcement Approach (ACRA) and MET/CBT5 when compared to MDFT in Trial 2. Sheidow et al. [202], computed Average Cost-Effectiveness Ratios (ACERS). ACERS only incorporate the pre-post treatment effect of one single treatment so treatments are not directly compared. Although this

study showed that Drug Court with community services (DC) was more cost effective compared to FC regarding substance use disorders and that the addition of multi-systemic therapy (MST) resulted in an economically more beneficial treatment, the treatments were not directly compared [202].

-Studies considering costs and benefits

Three of the studies that considered adolescents with substance use disorders, considered costs and benefits [197,199,207]. The study of French et al. [197] indicated that MET/CBT-5, MET/CBT-12 and FSN generated significant economic benefits to society for substance abusing adolescents, MDFT and ACRA did not generate these benefits. MCcollister et al. [199] showed that the savings in costs offset the treatment costs of DC, especially for DC/MST/ CM, in juvenile drug court participants when compared to FC (Family court with community services). Schoenwald [207] showed that the monetary benefits of MST compared to CAU for substance use disorder almost offset the higher costs of MDFT. Over time the difference between benefits and costs may be reduced to a complete offset.

Delinquency/externalizing disorders

Five studies considered adolescents with delinquency or externalizing disorders; the study of Sheidow et al. [198], Olsson [201], Cary et al. [203], Dopp et al. [205] and Borduin et al. [206] respectively included patients with a psychiatric crisis, patients with a conduct disorder, delinquent adolescents, serious juvenile offenders and juvenile sexual offenders. One study, Sheidow et al. [198], considered both costs and effects and four studies [201,203,205,206] considered both costs and benefits.

-Studies considering costs and effects

In the study of Sheidow et al. [198], MST was effective in the short term (4 months) in terms of externalizing behavior compared to care as usual for patients with psychiatric emergencies. But MST appeared equally effective on the cost measure over the long term (12 months).

-Studies considering costs and benefits

Olsson [201] showed that for adolescents with conduct disorder MST's benefits did not offset the costs and that MST was subsequently associated with a net loss to society. The study of Cary et al. [203] showed that MST in combination with CAU has a scope to generate cost savings when compared to providing CAU alone. The cost-

benefit study of Dopp et al. [205] indicated that MST, when delivered to serious juvenile offenders, produces economic benefits well into adulthood. Borduin et al. [206] showed that when juvenile sexual offenders are treated with MST-PSB; this treatment can produce lasting economic benefits.

Quality of the studies

Only for one study [198] commentary was available from the NHS-EED. We compared the commentary on the study with our quality assessment checklists to evaluate if all issues were addressed. The quality of the studies was not only assessed for the 7 unique studies but for the 9 studies. The argument for including all studies was to differentiate between methods (e.g. analysis), display of results and discussion even though they were based on the same study. The quality assessed with the BMJ checklist was between 52 and 86% (Table 7.5). The quality assessed with the CHEC list was between 50 and 79% (Table 7.5). Up to date, there are no thresholds (minimum number of criteria satisfied) for these checklists to determine the difference between bad and good quality economic evaluations [195]. Overall, the outcomes on the checklists matched although quality assessed with the CHEC list was consequently lower. The largest difference in quality percentages was 20%. All studies clearly stated their primary outcome measures. Most studies did not report all relevant costs and effects.

Table 7.5| Assessments of the quality of the studies with the Drummond checklist and the CHEC list

British Medical Journal Checklist	1*	2*	3*	4*	5*	6*	7*	8*	9*	10*	11*
1. The research question is stated.	-	-	✓	✓	✓	✓	✓	-	✓	✓	✓
2. The economic importance of the research question is stated.	✓	-	✓	✓	-	✓	✓	✓	✓	✓	✓
3. The viewpoint(s) of the analysis are clearly stated and justified.	-	✓	-	✓	-	-	✓	✓	-	-	-
4. The rationale for choosing alternative programmes or interventions compared is stated.	✓	-	-	-	-	-	✓	-	✓	-	-
5. The alternatives being compared are clearly described	✓	✓	✓	✓	-	-	-	-	✓	✓	✓
6. The form of economic evaluation used is stated.	-	✓	✓	✓	-	✓	✓	✓	✓	✓	✓
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	NC	✓	✓	✓	-	✓	✓	✓	✓	✓	✓
8. The source(s) of effectiveness estimates used are stated.	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
9. Details of the design and results of effectiveness study are given (if based on a single study).	✓	NA	✓	✓	✓	✓	✓	✓	-	✓	✓
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
12. Methods to value benefits are stated.	✓	✓	NA	✓	✓	NA	✓	NA	✓	✓	✓
13. Details of the subjects from whom valuations were obtained were given.	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
14. Productivity changes (if included) are reported separately.	NA	✓	NA	NA	NA	NA	NA	NA	NA	-	-
15. The relevance of productivity changes to the study question is discussed.	-	-	-	-	-	-	✓	-	-	-	-
16. Quantities of resource use are reported separately from their unit costs.	✓	✓	-	-	-	-	-	-	✓	✓	✓
17. Methods for the estimation of quantities and unit costs are described.	-	-	-	-	✓	-	✓	✓	✓	✓	✓
18. Currency and price data are recorded.	✓	✓	-	✓	-	-	-	✓	✓	✓	✓
19. Details of currency of price adjustments for inflation or currency conversion are given.	✓	✓	-	-	-	-	✓	-	✓	✓	✓
20. Details of any model used are given	NA	✓	✓	✓	✓	✓	NA	NA	✓	NA	NA

21. The choice of model used and the key parameters on which it is based are justified.	NA	-	-	✓	-	-	NA	NA	-	NA	NA
22. Time horizon of costs and benefits is stated.	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
23. The discount rate(s) is stated.	NA	NA	NA	NA	NA	NA	✓	NA	✓	✓	✓
24. The choice of discount rate(s) is justified.	NA	NA	NA	NA	NA	NA	✓	NA	✓	✓	✓
25. An explanation is given if costs and benefits are not discounted.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
26. Details of statistical tests and confidence intervals are given for stochastic data.	-	-	✓	-	✓	-	✓	✓	✓	-	-
27. The approach to sensitivity analysis is given.	✓	-	✓	-	-	-	✓	NC	✓	✓	✓
28. The choice of variables for sensitivity analysis is justified.	✓	NA	NA	NA	NA	NA	✓	NA	✓	✓	✓
29. The ranges over which the variables are varied are justified.	NC	NA	NA	NA	NA	NA	✓	NA	✓	✓	✓
30. Relevant alternatives are compared.	✓	NC	-	NC	✓	NS	✓	✓	✓	✓	✓
31. Incremental analysis is reported.	✓	✓	-	✓	✓	-	✓	-	✓	✓	✓
32. Major outcomes are presented in a disaggregated as well as aggregated form	✓	✓	✓	-	✓	✓	✓	✓	✓	✓	✓
33. The answer to the study question is given.	✓	NC	✓	✓	✓	✓	✓	✓	✓	✓	✓
34. Conclusions follow from the data reported.	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	-
35. Conclusions are accompanied by the appropriate caveats.	-	-	✓	✓	-	✓	✓	✓	-	✓	-
Total score British medical journal checklist (%)	68	61	63	68	54	52	86	70	83	81	77
CHEC list											
1. Is the study population clearly described?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2. Are competing alternatives clearly described?	✓	✓	✓	✓	-	-	-	-	✓	✓	✓
3. Is a well-defined research question posed in answerable form?	-	-	✓	✓	✓	✓	✓	-	✓	✓	✓
4. Is the economic study design appropriate to the stated objective?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
5. Is the chosen time horizon appropriate to include relevant costs and consequences?	NS	NS	✓	NS	NS	NS	✓	NS	NS	✓	✓
6. Is the actual perspective chosen appropriate?	-	✓	-	-	-	-	✓	-	-	-	-
7. Are all important and relevant costs for each alternative identified?	-	-	NS	-	-	-	-	-	-	✓	✓
8. Are all costs measured appropriately in physical units?	✓	✓	-	-	-	-	✓	-	✓	✓	✓

9. Are costs valued appropriately?	✓	✓	-	✓	✓	NS	✓	✓	✓	✓	✓
10. Are all important and relevant outcomes for each alternative identified?	-	-	✓	✓	-	✓	✓	✓	✓	✓	✓
11. Are all outcomes measured appropriately?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
12. Are outcomes valued appropriately?	-	✓	✓	✓	✓	✓	-	✓	✓	✓	✓
13. Is an incremental analysis of costs and outcomes of alternatives performed?	✓	✓	-	✓	✓	-	✓	-	✓	✓	✓
14. Are all future costs and outcomes discounted appropriately?	NA	NA	NA	NA	NA	NA	✓	NA	✓	✓	✓
15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	✓	-	-	-	-	-	✓	-	✓	✓	✓
16. Do the conclusions follow from the data reported?	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	-
17. Does the study discuss the generalizability of the results to other settings and patient/client groups?	-	-	✓	-	-	✓	✓	✓	-	-	-
18.Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	-	✓	-	-	-	-	-	-	-	-	-
19.Are ethical and distributional issues discussed appropriately?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Total score CHEC** (%)	56	67	61	61	50	50	79	50	79	74	74

*Studies: Schoenwald et al., 1996; 2 French et al., 2003; 3 Sheidow et al., 2004; 4 Dennis et al., 2004); 5 McCollister et al., 2009; 6 French et al., 2008; 7 Olsson, 2010; 8 Sheidow et al., 2012; 9 Cary et al., 2013; 10 Dopp et al., 2014; 11. Borduin et al., 2015. NS: Not stated; NA: Not applicable; NC: Not clear. Explanation criteria checklist: British medical journal checklist: 1.A specific question is not necessary, as long as the goal of the research is clearly stated; 5. The competing alternatives may also be described in a different accessible paper from the RCT in more detail 10. The presentation of the results is clearly given and discussions of the study contain generalizability and comparison with other studies. CHEC list: 5: Chosen time horizon is appropriate when after a certain time no additional effects are attained. **Scores were calculated by dividing the positively checked items on the quality checklist by the total minus items on the checklist that were not applicable (NA) to the study

Risk of bias

All studies were RCTs [197-207]. Two of these studies [198,207] only included patients receiving Medicaid (an aid program regarding insurances for low income families in the United States). For these studies, the RCT of the effect study contained (due to randomization) balanced samples. However, these samples were not checked for balance after the selection of participants who received medicaid, so they were at risk for selection bias. All studies had a high risk of performance bias, as blinding of both therapist and patient is impossible. For two studies [198,207] blinding was not necessary as both the cost and outcome data were extracted from existing data systems (The medicaid billing records). Although blinding of outcome assessors is possible to reduce detection bias, no study reported to have done so. Blinding is

also necessary for pre-allocation assessment. All studies were based on randomized controlled trials where allocation concealment is necessary. The studies included in this review, did not explicitly refer to the allocation concealment. Three studies were at risk of attrition bias. These three studies did not describe the number of patients that dropped out from the study [201,202,207]. Two studies only described the overall attrition rate [197,200]. For one study [204] however, overall attrition rate could be extracted by using the study of French et al. [197] as it was based on the same participants. Dropout in the effect-study of Sheidow et al. [198] was low and although no dropout was described for the economic evaluation, as the economic evaluation is based on the same participants, this is expected to be low. Overall, dropout rate (when measured) seemed low. Reporting bias was assessed by reading protocols from the studies and no bias was reported. Only for two studies [197,204] a protocol existed. Other studies did not have such a protocol, although for three studies trial registrations were present [199,201-203]. There were no indications of deviations from the original design. The economic evaluations did not always include all clinical outcomes that were available [198-200,207] as there was often only interest in specific outcomes. One study [200] excluded clinical outcomes as there was no difference between treatments in terms of outcomes and so only costs were considered (costs minimization). The exclusion of outcomes was not related to possible negative impact on the results as effects in the studies were equally or more beneficial when compared to the effects of the comparator.

Methodological summary

Uncertainty around treatment costs was not presented in four studies as averages of these costs were used [199,202,205,206]. In six studies [197,198,200,204-207] uncertainty around the (other) estimates was not (fully) addressed. In seven studies, a simple one way sensitivity analysis was used to assess the impact that changes in a certain parameter will have on the conclusions [197,198,201,203,205,206]. In two studies, sensitivity analysis was applied by imputing missing data in different ways. Outcomes proved to be robust [202,203]. Two studies performed scenario analyses meaning that cost estimates (surrounded by uncertainty) were increased or decreased. Data proved to be robust [201,207]. In another study a sensitivity analysis was carried out to assess the effect which outliers in each therapy group had on outcomes, but this did not have an effect the results. In the studies of Dopp et al. [205] and Borduin et al. [206] a sensitivity analysis was applied by using plausible minimum and maximum values

(obtained from other studies) for offense categories, arrest rates and discount rates. French et al. [197] used different models which assessed the effect on using more or less covariates in the models but it did not affect the results. In six of the studies cost-effectiveness/utility/benefits were assessed based on models [197-200,203,207]. Four of these studies used simple regression models [198-200,203] and two used a more advanced least squares random effect model [197,207]. The remaining three studies did not integrate any model in the analysis. Three studies did not report their price year (the year to which costs are indexed) [198,199,207]. Authors of three studies indicated that a societal perspective was adopted, where not only health care costs but also other costs, for example those associated with lost or impaired ability to work, were taken into account [197,201,204]. However, this was only true for the study of Olsson [201], as this was the only study to assess costs outside the health care sector. In the studies of Dennis et al. [204] and French et al. [197], the societal part was defined as using market values for calculating the costs of goods and services used. Dopp et al. [205] and Borduin et al. [206]conducted cost-benefit analyses and did not explicitly mention their perspective. Both studies focused on taxpayer benefits and expressed intangible benefits in monetary values. Cary et al. [203] used a narrow perspective as only services that were recorded by a specific data-system were included (appointments with social workers, connexion workers (a United Kingdom (UK) governmental information, advice, guidance and support service for young people aged thirteen to nineteen), reparation workers (coordinates and supports a range of interventions and community reparation projects that young people will have to undertake as part of their Referral or Community Order), parenting workers, group workers and psychologists). Sheidow [198] adopted the perspective of an institution. Other studies did not explicitly state their perspective. Most of the studies only reported treatment costs. A summary of the costs and clinical outcomes measured in the studies is provided in Table 7.6. Following Drummond et al. [209], full economic evaluations should not only report costs, but also health outcomes. Four studies were classified as cost-effectiveness analyses [198,200,202,204]. Only one of these studies compared treatments using an incremental cost-effectiveness ratio [204] as described for instance by Drummond et al. [209]. The cost-effectiveness analysis of French et al. [200] was reduced to a simple cost minimization analysis as the effects of both treatments after analysis proved to be similar. Sheidow et al. [202] calculated average cost-effectiveness ratios (ACER), which means that there was no direct comparison between treatments but only between the before- and after treatment costs and effects of every participant. In

four studies it was explicitly stated that cost-benefit analyses [197,201,205,206] were performed. Olsson [201] considered psychosocial and behavioral effects, but as no difference was observed regarding these clinical measures between treatments, these effects were excluded from the analysis. French et al. [197] did not value the health outcomes on which the intervention was focused (like reduction in days of substance use) but did value the effects of treatment on education, employment and criminal activity. Dopp et al. [205] and Borduin et al. [206] conducted a cost-benefit analysis; the cost outcome were the treatment costs and the benefits were defined as taypayer benefits, tangible benefits and intangible benefits were expressed in monetary values. Cary et al. [203] classified his study as a cost-offset evaluation. He calculated the net-benefit, but stated that his study cannot be viewed as a cost-effectiveness study as he did not measure health outcome. Two studies did not state the type of economic analyses they performed [199,207], but did consider both costs and benefits. Mcollister [199] indicated that her study was not a full economic evaluation, as she only considered treatment costs. This is also the case concerning the study of Sheidow et al. [202], however, this study was stated to be a cost-effectiveness analysis. Furthermore, Schoenwald et al. [207] did not classify their study explicitly but considered both costs of different health care services and monetary benefits so it can be considered a cost-benefit analysis.

Table 7.6|Overview of costs and clinical outcome measures used in studies

	Treat-ment costs	Other health-care costs	Costs outside health care sector	Perspective used in the economic evaluations	Clinical outcome measure
(Schoenwald et al., 1996)	✓	✓		Healthcare	-
(French et al., 2003)	✓			Institution	-
(Sheidow et al., 2004)	✓	✓		Healthcare	CBCL/GSI
(Dennis et al., 2004)	✓			Institution	-
(McCollister et al., 2009)	✓			Institution	SRD
(French et al., 2008)	✓			Institution	YSR/days of marijuana use
(Olsson, 2010)	✓		✓	Societal	-
(Sheidow et al., 2012)	✓			Institution	TLFB/SRD
(Cary et al., 2013)	✓			Institution	-
(Dopp et al. 2014)	✓		✓	Societal	-
(Borduin et al. 2015)	✓		✓	Societal	-

CBCL=Child Behavior Checklist; GSI: Global severity index; SRD=Self-Report Deliquency Scale; TLFB=Timeline Follow-back Form; YSR=Youth Self Report

Limitation/generalizability summary

Four studies commented on their generalizability [198,200-202]. Sheidow et al. [198] reported that as their sample only consisted of youths enrolled in Medicaid, which are generally economically less advantaged, findings cannot be generalized to a more economically advantaged population. The same is true, although not stated, for the study of Schoenwald et al. [207] who also analyzed Medicaid data. The study of Olsson [201] was conducted in Sweden, where MST is twice more expensive than in the USA and may play a different role in society. MST in Sweden may be used as an alternative to nonplacement interventions as opposed to an alternative to

placement interventions as found in other studies. Also in the study of French et al. [200], which was conducted in Mexico, location and small sample size were indicated as limitations for generalizability. The same was true, although not stated, for the study of Cary et al. [203] which was conducted in the United Kingdom. Also an important limitation (but not mentioned as such) were the omissions of uncertainty around the estimates in the studies of Dopp et al. [205] and Borduin et al. [206], so the results should be interpreted with caution. Furthermore, the study of Borduin et al. [206] was based on a very small (the smallest one in this review) sample size (only 48 patients) so uncertainty around the estimates (not reported) is expected to be high. Sensitivity analysis is not a solution for this problem as significance of the results cannot be determined (as the estimates in the sensitivity analysis are also subjected to uncertainty). The juvenile drug court programs, analyzed in the study of Sheidow et al. [202] are not easily generalized to other settings as they show great variation due to absence of a strict format. In addition, other settings may have different populations and salaries implying differences in costs. Almost all studies were cautious with drawing conclusions on their data. They not only recognized limitations within their research but also recognized that the number of economic evaluations is very limited and more research is needed before being able to draw conclusions [197,198,200-203,207,208].

Meta analysis

The data from the economic evaluations were not pooled as the population, setting, outcomes, costs and interventions were not comparable across studies.

7.4 DISCUSSION

This systematic review summarized and evaluated the cost-effectiveness of family/family-based therapy for adolescents with externalizing disorders, substance use disorder and delinquency. The overall quality of these studies was low, they produced mixed results. Research should consider a wider perspective and take into account all relevant costs and effects using sophisticated models. Studies evaluating family/family based therapy concerned various outcomes and costs, and investigated a variety of treatments in various populations in different settings. Therefore it was not possible to conduct a meta-analysis. As expected, most of the studies were conducted in the United States where family/family-based treatments originate from [35,36,210]. The findings cannot be easily generalized to other health care systems as they differ between countries. The quality assessments showed that overall studies scored between 50 and 86% and only two studies scored higher than 80% [201,203,205,206]. Studies that were conducted more recently, were in general higher of quality. When the two most recent studies [205,206] were not considered, the quality of the studies overall was slightly higher for those studies originating from Europe. The quality of the two most recent studies was high when using the quality checklists, however, they also contained some important limitations. Firstly, although quality checklists only contain one question with respect to uncertainty around the estimates, it can be of paramount importance, especially when the sample size is low. Secondly, these studies are not easily generalized to an European setting as they conducted cost-benefit analyses, opposed to cost-effectiveness analyses that are commonly applied in European studies. Although the checklists used to assess quality of the studies depend on the subjective evaluation of the researchers and have yet not been validated, these two checklists have received much scrutiny and are therefore recommended [195]. Recommendations that follow from the quality assessment of the studies that were included in the review, are the following. Different treatments that are included in the study should be described more clearly so the differences and similarities between treatments are understandable. In many of the studies included in the review, the perspective taken was not mentioned or did not match with the categories of the costs that were included. In line with guidelines for economic evaluations the perspective should be stated [209]. A more broad perspective (societal versus healthcare) is recommended. The unit costs and resource use should be reported separately and a source of the references for the

unit costs should be given. It is also important to explicitly mention whether a study is considered a cost-effectiveness/cost-benefit or cost-utility analysis. Most studies included in the review used no model or simple models (regression). More complex models, like multilevel analysis, should be used. In this way covariates can be included, correlation between measurements over time can be addressed, missing data is accounted for and skewness in the costs and effects is considered. Uncertainty around costs should also be presented by using for instance bootstrapped costs/effects confidence intervals and can be visualized in a cost-effectiveness plane. Sensitivity analysis should be applied to variables that are uncertain (the rationale behind it should be explained). A one way sensitivity analysis is not always sufficient and a sensitivity analysis also taking into account interactions between variables should be considered. A common discount rate should be applied for all costs and effects. Summary measures of the cost-benefit, cost-effectiveness or cost utility should be given. In case of a cost-effectiveness analysis incremental cost-effectiveness ratio (ICERS) should be calculated. For conducting economic evaluations it is advised to consult a health economist.

Conclusions

Although family/family-based treatments are widely used and can be considered as effective for the treatment of a wide range of disorders [194], cost-effectiveness also needs to be addressed. Taking cost-effectiveness into account may have a large impact as family/family-based treatments are expensive. This review has summarized the economic evidence of family/family-based therapy for substance use disorders and delinquency in adolescents in a systematic and transparent way by using state of the art guidelines [52,195]. As there are few studies evaluating the cost-effectiveness of family/family-based therapy and the quality of the existing studies is limited, new studies using higher quality standards are necessary. Large-scale implementation of these treatment models should be held back, until more evidence is available.

Appendix 7.1.

Table 7.7| Description family/family-based interventions

Family/Family based interventions	
MST	Target family interaction and the extended social systems in youths with substance abuse problems, delinquency or antisocial behavior / Permits separate meetings adolescent but preference for family /More focus on antisocial behavior/ focused both on family functioning and on extra familial functioning / Treatment team not actively involved as observers and actors but team is only self-reflexive/ Treatment team actively involved as observers and actors /degree of severity higher and combination of more problems
FFT	Target family interaction and the extended social systems in youths with substance abuse problems, delinquency or antisocial behavior/ Almost no separate meetings adolescent /More focus on antisocial behavior/More focused on family functioning less on extra familial functioning/ Treatment team not actively involved as observers and actors but team is only self-reflexive/ explicitly emphasizes therapist is integral part of the system/degree of severity lower
MDFT	Target family interaction and the extended social systems in youths with substance abuse problems, delinquency or antisocial behavior/ Separate meetings adolescent/ Focus on substance abuse / focused both on family functioning and on extra familial functioning /Treatment team not actively involved as observers and actors but team is only self-reflexive/degree of severity higher

Sources: Leukehof et al. and Oudhof et al. [211,212] Legend: MST=multisystemic therapy; FFT= functional family therapy; MDFT= multidimensional family treatment

Appendix 7.2

Search terms Pubmed

"family therapy"[MESH]
"Functional family therapy"
(FFT NOT ("fast Fourier transform" OR "freedom-from-transfusion" OR "fast Fourier transforms" OR "fast Fourier transformation" OR "Far-Field Transform"))
"Multisystemic Therapy"
(MST NOT ("microbial source tracking" OR "minimum spanning tree"))
"Multidimensional Treatment Foster Care"
"MTFC"
"multidimensional family therapy"
"MDFT"
"family behavior therapy"
"FBT"
brief strategic family therapy"
"BSFT"
"family based therapy"[Title/Abstract]
"family based interventions"[Title/Abstract]
"family based intervention"[Title/Abstract]
"family systems intervention" [Title/Abstract]
"family systems interventions" [Title/Abstract]
"family system intervention" [Title/Abstract]
"family system interventions" [Title/Abstract]
"family intervention program"[Title/Abstract]
"family intervention programs"[Title/Abstract]
"systemic Therapy" [Title/Abstract]
OR 1-23
"economic evaluation" [title/Abstract]
"economic evaluations" [title/Abstract]
"cost effective" [title/Abstract]
"cost effectiveness" [title/Abstract]
"cost utility analysis" [title/Abstract]
"costs" [Title/Abstract] AND "effect"[Title/Abstract]
"cost" [Title/Abstract] AND "effect"[Title/Abstract]
"cost" [Title/Abstract] AND "effects"[Title/Abstract]
"costs" [Title/Abstract] AND "effects"[Title/Abstract]

"costs"[Title/Abstract] AND "benefits"[Title/Abstract]
"cost" [Title/Abstract] AND "benefit"[Title/Abstract]
"costs" [Title/Abstract] AND "benefit"[Title/Abstract]
"cost" [Title/Abstract] AND "benefits"[Title/Abstract]
"costs" [Title/Abstract] AND "utility"[Title/Abstract])
"cost" [Title/Abstract] AND "utility"[Title/Abstract])
"cost" [Title/Abstract] AND "utilities"[Title/Abstract]
"costs" [Title/Abstract] AND "utilities"[Title/Abstract])
"Cost Analysis" [title/Abstract]
"Cost Measures" [title/Abstract]
"cost benefit analysis"[title/Abstract]
"cost measure" [title/Abstract]
"cost" [title]
"costs" [title]
"cost benefit analysis" [MESH]
OR 25-48
NOT (cancer[Title/Abstract]OR psoriasis[Title/Abstract]OR "radiation therapy"[Title/Abstract] OR diabetes[Title/Abstract] OR diabetic[Title/Abstract] OR obesity [Title/Abstract] OR aids[Title/Abstract] OR HIV[Title/Abstract] OR sarcomas[Title/Abstract] OR chemotherapy[title/Abstract]))
24 AND 49 AND 50
Search terms Eric, Psycinfo and Cochrane
In Eric, the same search terms were used except for the MESH terms. In psycinfo, the MESH terms were replaced with APA's thesaurus of Psychological index Terms and in cochrane, the same terms were used.

8 COST-EFFECTIVENESS OF MULTIDIMENSIONAL FAMILY THERAPY COMPARED TO COGNITIVE BEHAVIORAL THERAPY FOR ADOLESCENTS WITH A CANNABIS USE DISORDER: DATA FROM A RANDOMIZED CONTROLLED TRIAL

Based on: Goorden M., Schee van der E., Hendriks V.M., Hakkaart-van Roijen L. (2016). Cost-effectiveness of multidimensional family therapy compared to cognitive behavioral therapy for adolescents with a cannabis use disorder: Data from a randomized controlled trial. Drug and Alcohol Dependence, 162:154-161.

Abstract

Objective: To evaluate the cost-effectiveness of Multidimensional Family Therapy (MDFT) for adolescents with a cannabis use disorder, compared to Cognitive Behavioural Therapy(CBT).

Methods: A parallel-group randomized controlled trial was performed. 109 adolescents with a DSM-IV cannabis use disorder (CBT n = 54; MDFT n = 55) were included. Assessments were conducted at baseline, and 3, 6, 9 and 12 months post-baseline, and included measures on cannabis and other substance use, delinquency, health care utilization, and general health related quality of life.

Results: Excluding those with missing cost-data, 96 participants (MDFT n = 49; CBT n = 47) were included. From a health care perspective, the average annual direct medical costs in the CBT group were €2015 (95% C.I. 1397–2714), compared to €5446 (95% C.I. 4159–7092) in the MDFT group. The average quality-adjusted life years (QALY's) gained were 0.06 QALY higher for the MDFT group, which led to an incremental cost-effectiveness ratio (ICER) of 54,308 Euro/QALY or €43,405 per recovered patient. Taking the costs of delinquency into account, the costs increased to €21,330 (95% C.I. 12,389–32,894) for the CBT group and to €21,915 (95% C.I. 16,273–28,181) for the MDFT group, which lead to an ICER of 9266 Euro/QALY or a cost per recovered patient of €7491.

Conclusions: This is the first comprehensive CEA of MDFT compared to CBT and it demonstrated that when costs of delinquency were included, the ICERS were modest. The results underline the importance of adopting a broader perspective regarding cost effectiveness analyses in mental health care.

8.1 INTRODUCTION

In the Netherlands, individual Cognitive Behavioral Therapy (CBT) is the first choice psychosocial treatment for substance abusing adolescents. However, environmental factors, like substance abusing peers and parent-child relationship, also influence substance abusing adolescents [184,185,187] need to be addressed in therapy. Multidimensional Family Therapy (MDFT) is a promising treatment, as it not only targets the individual but also the systems surrounding the individual. In a meta-analysis that evaluated the effectiveness of outpatient substance abuse treatments for adolescents, family therapy was the most convincing and consistent effective treatment for substance abuse, and although CBT was more effective than any other nonfamily treatment, family therapy was superior [213]. Based on these findings, family therapy is the treatment with the strongest evidence of comparative effectiveness, although most types of treatment appear to be beneficial in helping adolescents reduce their substance use. A randomized controlled study in the Netherlands showed that MDFT and CBT were equally effective in reducing cannabis use and delinquent behavior in adolescents with a cannabis use disorder [192]. Regarding cost-effectiveness, only a limited number of studies assessed family interventions in adolescents. To date, there is one randomized trial that showed that MDFT was more costly and was equal in clinical effectiveness compared to CBT [204]. This study was limited to the monetary benefits compared on two clinical outcomes: days of abstinence after 12 months and 'being in recovery' at the end of the study (defined by the authors as being abstinent and living in the community). In addition, as the study was conducted in the United States, the study findings cannot be generalized to the Dutch healthcare system without any consideration. Although studies evaluating the cost-effectiveness for MDFT are limited, the interest in cost-effectiveness analyses for relative expensive but commonly applied family treatments is strongly increasing as they compete with other (medical) treatments for health care budgets. Next to difference in health care costs, cost savings may result from a decrease of adolescent criminal behavior. Cannabis and other substance use disorders in adolescents often coincide with delinquent behavior [214]. This relationship may reflect a common predisposition to addiction and delinquency, related to certain personality characteristics (e.g., impulsivity) and associated genetic factors [215], decreased inhibitory control as a result of the acute effects of psychoactive substances or of chronic substance use [216],an increased probability to commit crimes, to obtain

money for buying drugs [217], as well as the influence of deviant peer affiliations on crime and substance use in adolescent [218]. In any case, costs related to criminal involvement are important to include in a cost-effectiveness study of substance abuse treatment in adolescents. The aim of the present study was to evaluate the cost-effectiveness of MDFT versus CBT in adolescents with a cannabis use disorder from a health care perspective. Additionally, the cost-effectiveness was assessed by including the costs of delinquency. We performed a cost-utility analysis, which has the advantage over a more general cost-effectiveness study in that the intervention is also comparable to interventions outside the mental health care system by using a generic outcome measure (quality of life). In addition, when treatments are equal in clinical effectiveness a cost utility study may add extra information on decisions for policymakers. Additionally we performed a cost-effectiveness analysis using a clinical outcome measure.

8.2 METHODS

General study design

The cost-effectiveness analysis was conducted on data pertaining to the parallel-group randomized controlled study of Hendriks et al. [192]. This study was approved by the medical-ethical committee for research in mental health care settings of The Netherlands (METiGG; registration nr. 5238). This study was performed from March 2006 until October 2010 and evaluated the effectiveness of MDFT versus CBT. Eligible patients were randomly allocated (ratio 1:1) by the research group by using a computer-generated randomization list. Sample size calculation was based on Monte Carlo simulation techniques and resulted in a minimum of 100 and a maximum of 120 participants. Randomization was concealed and was conducted separately for the two study sites, and prestratified for age (13–14 vs. 15–18 years old), gender, ethnicity (Dutch/western vs. other) and frequency of cannabis use (< 75 days vs. ≥75 days in the previous 90 days), using blocks of two patients.

Participants

Adolescents (13–18 years old) with a cannabis use disorder who applied for treatment at two treatment sites in The Hague were screened. The following inclusion criteria were used: using cannabis for at least 26 days in the 90 days before baseline, meeting the DSM-IV diagnostic criteria for past year cannabis abuse or dependence, and written informed consent. In this trial, 109 participants were included (CBT n = 54; MDFT n = 55). The detailed study protocol and results of this trial have been described elsewhere [192,219].

Treatments

MDFT

The intervention involved individual outpatient therapy and sessions with the parents and/or family, twice a week, 1 h each, for 5–6 months. MDFT is not only aimed at the individual but also at the relationship with parents, family members or other extra-familial relevant contacts so extra-familial sessions involving school, work, drug using peers, the court and the juvenile justice system were arranged if necessary. Therapists were trained by the developers of MDFT in the United States and the original manual of MDFT was used during therapy [33]. In addition, trainers were contacted monthly, to receive feedback and consultation.

CBT (care as usual)

CBT consisted of individual outpatient sessions, once a week, 1 h each, for 5–6 months. A non-system-oriented session to provide parents with information and support was held once a month. The first four sessions focussed on enhancing treatment motivation, building rapport, determining treatment goals and conducting an initial functional analysis. Until the 12th session, the main goal of treatment was to develop skills and achieve and maintain abstinence from cannabis. After this, treatment focussed on topics indirectly related to maintaining abstinence. The duration of treatment was also 5–6 months, to synchronize with MDFT. Therapists were trained and used a manual based on the Cannabis Youth Treatment (CYT) study [204,220,221].

Outcome measure and assessments

The total duration of the study was 1 year (5–6 months treatment and 6–7 months of follow up). Data were collected by independent research assistants. Cost-effectiveness was determined by evaluating the quality of life and whether a person was in 'recovery', and by calculating the direct medical costs and costs related to delinquency. Data on quality of life was collected at baseline, 6, 9 and 12 months, data on the health care costs at 6 and 12 months and costs related to delinquency were collected at baseline, 3, 6, 9 and 12 months. The primary outcome measure was costs per quality-adjusted life year (QALY). Recovery was a secondary outcome measure and was based on the definition as used in the original trial of Hendriks et al.[192].

Quality of life and recovery

Quality of life was assessed with the Euroqol 5 Dimensions [10]. The EQ- 5D is a standardized, validated instrument and encompasses five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated by the patient on three levels (no problems, some problems, and extreme problems). Thus, 243 distinct health states are defined, each with a unique utility score, ranging from 1 (perfect health) to 0 ('death'). Adolescents were considered to be 'in recovery' if they lived in the community and were abstinent from cannabis, heavy alcohol use (≥5 glasses a day) and any other substance use in the 30 days preceding the month 12 assessment. 2.4.2.

Direct medical costs

Direct medical costs were measured with the Treatment Inventory of Costs in Psychiatric Patients (TiCP), a validated instrument [13] that records self-reported number of contacts with health care providers during the previous three months. Unit costs were valued according to prices reported in the Dutch manual for cost research [86] so the costs can be obtained by multiplying the unit prices with the volume. The costs of the MDFT and CBT therapists were based on the gross wages per year, working hours, session length of 1 h, preparation and writing of reports, overhead and bonus, and education costs for both therapies. All unit costs were corrected for inflation.

Costs related to delinquency

To include costs related to delinquency, the Self Reported Delinquency (SRD) questionnaire was administered [222]. This questionnaire consists of questions aimed at mapping delinquent behavior in adolescents. Questions are categorized into: Internet offenses, drug offenses, discrimination, destruction/public order offenses, property offenses, traffic offenses and aggression, violent offenses and sex offenses. In each item of the questionnaire, the adolescent is asked at what age he or she first engaged in the specified delinquent behavior and the number of times this behavior was performed in the last 90 days. This number is translated into costs by specifying unit prices, which subsequently can be multiplied by the volumes to obtain costs. Unit prices are not yet available, so we estimated these costs based on two different sources [223,224]. The Research and Documentation Centre (WODC) of the Netherlands provided an overview for expenses made for prevention, tracing, prosecution, going on trial, execution of verdict, support of suspects and perpetrators, support of victims, consulting of legal experts and other activities in The Netherlands. We matched the expense categories used by the WODC with the categories used in the SRD.As the expenses on support for suspects were already included in our health care costs, these were subtracted from the total costs. The WODC (2012) also provided the number of registered crimes, the number of suspects for certain crimes and the percentage of crimes that is registered (based on victim reports), so registered criminality could be corrected for multiple suspects and probability of not being detected. As percentage of crimes that are registered for traffic offenses were not included in the Figures of the WODC, instead, the subjective chance of getting caught was used which was obtained from a different source[224]). These were added for

different categories of criminal behavior according to the SRD. Additionally they provided the number of registered crimes that were subsequently adjusted for probability of registration of the crime and multiple suspects. For acquiring the unit costs, the total costs were divided by the total (adjusted) number of crimes and were subsequently indexed.

Data analysis

Ninety-six adolescents (MDFT: 49; CBT: 47) were included in the study. As described in the paper of Hendriks et al. [192], at month 9, the missing completely at random assumption (MCAR) was violated, and these data were subsequently excluded from the analyses. Patients were removed from analysis when there was insufficient information available regarding costs and effects, 1 measurement moment. As a result, a total of 13 adolescents were excluded from the analyses. The health descriptions from the EQ-5D used to measure health-related quality of life were linked to empirical valuations of the Dutch general public, allowing utilities to be computed. Utilities are index based values that reflect the preference of one state to another. To obtain one utility score per patient, the area-under the curve method (AUC) was applied[11]. To obtain one utility per patient, the area under the curve of the utilities over the different points in time was determined using the Riemann sum. To calculate the incremental utilities; the utilities of the treatment groups (MDFT and CBT) were subtracted. The numbers of missing values of the utilities at baseline and at the end of treatment were both low (0% and 7%, respectively). As there were more missing values in between (51% after 6 months), the missing utility values at 6 and 12 months were estimated by interpolation. Interpolation is a method used to construct new data points within the range of a set of known data points using a (in this case) linear function. Health care costs and costs related to delinquency were determined by multiplying the number of treatment contacts/number of crimes (over 3 months) by the reference unit prices of these services or crimes. For adolescents, health care use in general is low as they are, inherent to their age, generally healthier than adults. Based on this characteristic and the data distribution (frequency of zero's ranged from 65 to 100%), missing values at 6 months (36.5%) and 12 months (3.1%) were imputed with a zero value, meaning no costs. We did not perform a sensitivity analysis on the effect of the zero "imputations" as our dataset would become very small and we believe this would not add to a more accurate analysis." A model predicting missing values more precisely cannot be generated as the discrete number of

values is low because the data contained a lot of patients with zero costs (point mass is zero). To obtain health care costs for half a year, costs acquired by the TIC-P, covering 3 months, were doubled. The SRD did not provide a distinction between offenses that were committed by car or offenses committed by bike (although the difference in costs between these type of offenses is high). Therefore, information from the remarks of the SRD, was assessed to distinguish between these types of offenses. However, these remarks did not always contain this information. In addition, there was uncertainty about the probability of getting caught in traffic offenses and subsequently uncertainty in the unit costs. Therefore, there was much uncertainty around the costs of traffic offenses and a sensitivity analysis was performed, omitting these costs. The uncertainty in the analysis was assessed using nonparametric bootstrapping (5000 times). This was expressed in a cost-effectiveness acceptability curve. The acceptability curve illustrates the probability that the cost-effectiveness ratio will be accepted for different cost limits (using the bootstrapped values) given a societal willingness to pay threshold. Including the costs of delinquency, the procedure was repeated. An incremental cost-effectiveness ratio (ICER) was calculated to obtain the costs per quality Adjusted Life Year (QALY). The ICER was calculated by dividing the incremental costs by the incremental effects and represents the cost to achieve a unit of improved outcome in the intervention relatively to its comparator. The incremental costs per recovered patient were also calculated by dividing the incremental costs by the incremental number of recovered patients. Analyses were conducted using the Statistical Package for the Social Sciences 19.0 (SPSS 19.0) and Excel (2010).

8.3 RESULTS

Demographics

The (consort) flow diagram in the Appendix 8.1 describes the participant flow. The trial was ended within the planned 22 weeks treatment period and 1 year total study period. Table 8.1 summarizes the baseline demographic and clinical patient characteristics for the MDFT group and CBT group. At baseline, there were no significant differences between both groups.

Table 8.1| Sample characteristics at baseline

	MDFT*(N=49)	CBT*(N=47)
	Mean (SD)/Percentage (%)	Mean (SD)/Percentage (%)
Age	16.7 (1.32)	17.0 (1.19)
Gender male (%)	77.6	76. 6
Ethnicity (Dutch) (%)	72.3	72.7
Age of onset cannabis use	14.27 (1.50)	14.38 (1.34)
EQ-5D adolescents	0.88 (0.15)	0.89 (0.13)
Cannabis use past 90 days (#days)	61.7 (23.0)	62.5 (23.8)
Cannabis use past 90 days (#joints)	157.0 (119.5)	159.9 (133.4)
Cannabis dependence (%)	81.6	78.7
Ever convicted by court (%)	51.0	51.1
Parents living together (%)	38.8	40.4
Ever been in substance abuse treatment (%)	10.2	10.9
Ever been in psychiatric treatment (%)	34.8	37.0
Destruction and/public offenses past 90 days(#times)	32.5 (51.2)	19.9 (33.3)
Traffic offenses past 90 days (#times)	22.2 (36.1)	24.6 (36.7)
Aggression and violent offenses past 90 days (#times)	14.6 (30.1)	12.1 (26.4)

*MDFT=Multidimensional Family Therapy; CBT=Cognitive Behavioral Therapy; SD=Standard Deviation

Quality of life/recovery

Quality of life at baseline was 0.89 (0.13) for the CBT group and 0.88 (0.15) for the MDFT group. The improvement in quality of life (EQ-5D) over time (effect,

calculated with the AUC method) was −0.02 for the CBT group (95% C.I., −0.05 to 0.02) and 0.04 for the MDFT group (95% C.I., 0.03–0.06),indicating that quality of life was not affected in CBT, but was improved in MDFT. The difference in improvement between both groups over time was 0.06 (95% C.I., 0.03–0.10). Over time the decrease in problems on the EQ-5D dimension pain/discomfort was higher (35% at baseline indicated no problems and 11% after 12 months) in the MDFT group than in the CBT group (23% at baseline indicated no problems and 16% after 12 months). Anxiety/depression also decreased more in the MDFT group (28% at baseline indicated no problems and 4% after 12 months) than in the CBT group (25% at baseline indicated no problems and 20% after 12 months). However, daily activities improved more in the CBT group (32% at baseline indicated no problems and 7% after 12 months) than in the MDFT group (20% at baseline indicated no problems and 13% after 12 months). The percentage of recovered patients after 12 months was 6.4% for the CBT group and 14.3% for the MDFT group. The difference in effects was not significant, $*2(1, N = 96) = 1.606$, $p = 0.205$. The relative risk was 2.2, so the chance of recovery in the MDFT group was (although not significant) approximately twice as high as the chance of recovery in the CBT group.

Direct medical costs

The most relevant unit prices are summarized in Table 8.2. The costs of the MDFT and CBT therapists were based on the gross average wages per year (which were the same for both CBT and MDFT therapist) of€38,740, the working hours (1540), the session length of 1 h, the preparation and the writing of reports of both 20 min, overhead and bonus, and the education costs for both therapies. Including all therapist-related costs, the cost of one MDFT session was estimated at €67 and the costs of one CBT session at€66. The total average annual direct medical costs were €2015 (2807) for the CBT group. These costs were significantly higher for the MDFT group: €5446 (8032), mainly due to significantly higher treatment costs of MDFT treatment (see Table 8.3). Costs associated with (psychiatric) hospital admissions were higher in the MDFT group. However, costs associated with (additional) mental health care were higher in the CBT group.

Table 8.2|Unit costs-2009, sorted by height of costs, source (excluding therapists): Dutch manual for cost research [86]

Category	Unit price (€)
(psychiatric) hospital day	232
Mental Health Care Institute contact	171
Medical Specialist contact	96.50
MDFT contact	67
CBT contact	66
Social Worker contact	65
Occupational physician contact	57
Alternative medicine contact	55
Paramedical contact	36
GP contact	28

Table 8.3|Mean annual cost per adolescent for both treatments based on unit prices of 2012

	MDFT*(N=49)			CBT*(N=47)		
	Mean costs (€,SD)	Percentage of total costs (%)	Percentage of patients (%)	Mean costs (€, SD)	Percentage of total costs (%)	Percentage of patients (%)
MDFT therapy/ CBT therapy*	3,372 (1,401)	62	98**	896 (820)	44	89
(psychiatric) hospital days	1,610 (7,327)	30	8	456(2181)	23	6
Social Worker	173(462)	3	33	112 (276)	6	23
General practitioner	46 (65)	1	49	41 (59)	2	40
Medication	28 (79)	1	31	13 (43)	1	21
Medical Specialist	58 (121)	1	27	83 (194)	4	23
Paramedic care	49 (188)	1	10	7 (34)	0	4
Mental Health Care	80 (430)	1	4	317 (80)	16	13
psychologist/psychiatrist	20 (87)	0	4	12 (59)	1	4
Counselling centre for drugs alcohol	9 (66)	0	2	1 (8)	0	2
Occupational physician	1 (8)	0	2	1(8)	0	2
Alternative medicine	0(0)	0	0	28 (185)	1	2
Selfhelp group	0(0)	0	0	49 (334)	2	2
(parttime) day care	0(0)	0	0	0(0)	0	0
Total costs	€5,446 (8,032)			2,015 (2,807)		

*MDFT=Multidimensional Family Therapy; CBT=Cognitive Behavioral Therapy; SD=Standard Deviation. **There was 1 person who did not start treatment

Costs related to delinquency

An overview of the unit costs of delinquency is given in Table 8.4. The mean number of self-reported illegal activities categorized by type of offense in the past 90 days and associated annual costs are presented in Table 8.5. The total annual costs were €16,469 (30,900) in the MDFT group and €19,314 (42,916) in the CBT group. Especially costs associated with traffic offenses (unauthorized driving, driving under influence and other traffic offenses) were higher in the CBT group.

Table 8.4| Delinquency unit costs in 2012

Category	Unit price (€)*
Robbery and theft with violence	20,939
Simple and aggravated assault	4,234
Simple theft/picket pocketing	1,960
Destruction/vandalism of private/public property	1,910
Threat	1,819
Forced sexual contacts	1,734
Receiving	1,694
Arson	1,449
Traffic offenses: Unauthorized driving	975
Traffic offenses: Driving under influence	213
Selling Harddrugs**	130
Discrimination	108
Nuisance	108
Selling softdrugs[2]	41
General Traffic offenses	3

*The unit costs contain costs of prevention, tracing, prosecution, going on trial, execution of verdict , support of suspects and perpetrators, support of victims, consulting legal experts and other activities

**In the Netherlands we make a distinction between soft drugs and hard drugs. Soft drugs are drugs that are less inhibiting and addicting than hard drugs, often being defined as causing psychological, but not physical addiction. Hard drugs are often defined as being both physically and psychologically addictive, while also posing serious risks to users.

Table 8.5| Mean number of times of engagement in illegal activity categorized by type of offense and associated costs for adolescents for both treatments in one year

	MDFT* (N=49)		CBT* (N=47)	
	Number of times engaged 1 year (SD)	Average costs (€, SD) per adolescent	Number of times engaged 1 year (SD)*	Average costs (€,SD) per adolescent
Drug offenses	15.4 (38.0)	852 (2,305)	4.9 (15.6)	556 (2,008)
Selling softdrugs	12.9 (35.7)	529 (1,462)	0.9 (3.0)	38 (123)
Selling harddrugs	2.5 (14.0)	324 (1,818)	4.0 (15,5)	518 (2,009)
Discrimination	0.3 (0.8)	26 (84)	0.1 (0.3)	7 (27)
Calling names	0.3 (0.8)	26 (84)	0.1 (0.3)	7 (27)
Fighting	0 (0)	0 (0)	0(0)	0 (0)
Destruction/public order offenses	45.6 (65.8)		35.2 (60.6)	
Nuisance	9.2 (30.1)	923 (3007)	2.6 (3.5)	260 (350)
Destruction private property	0.0 (0.2)	2,846 (9,209)	0.1 (0.3)	1,666 (7,542)
Destruction public objects	0.1 (0.4)		0.1 (0.3)	
Vandalism public or private objects	1.3 (4.4)		0.7 (3.8)	
Fare dodging	33.9 (55.6)		30.8 (56.2)	
Fire work offense	0.8 (2.7)		0.9 (3.0)	
Arson	0.2 (0.8)	296(1,145)	0.1 (0.4)	154(543)
Property offenses	3.1 (5.4)	5,849(10,272)	3.5 (8.9)	6,665 (17,119)
Simple theft	2.0 (3.9)	3,920 (7,706)	2.8 (7.7)	5,470 (15,036)
Shop	0.9 (2.6)	1,840 (5,192)	0.8 (2.6)	1,585 (5,164)
School/work	0.3 (1.0)	640(2,016)	1.8 (7.0)	3,593 (13,629)
Without break-in private objects	0.7 (2.1)	1,440 (4,192)	0.2 (0.5)	292 (999)
Theft with or without break-in with or without theft	0.1 (0.4)	200 (721)	0.0 (0.2)	42 (286)
Receiving	1.0 (2.9)	1,729 (4,872)	0.7 (2.2)	1,153 (3,656)
Traffic offenses	39.4 (67.0)	410 (870)	27.5 (59.3)	3,975 (23,426)
Unauthorized driving	0.3 (0.8)	268.6 (802.7)	3.3 (19.7)	3,226 (19,230)
Driving under influence	0.1 (0.3)	23.9 (73.0)	3.2 (19.7)	686.6 (4203)
General	39.0 (66.9)	117.1 (200.6)	20.9 (45.1)	62.7 (136)
Aggression and violent offenses	14.4 (39.8)		13.5 (36.3)	
Threat	0.4 (1.1)	742 (1,962)	0.3 (0.7)	581 (1,320)
Pocket-picking	0.1 (0.2)	120 (475)	0.0 (0.2)	42 (286)
Robbery/theft with violence	0.0 (0.1)	427 (2,991)	0 (0)	0(0)
Weapon possession	13.0 (39.6)			
Simple or aggravated assault	0.9 (2.7)	3,975 (11,544)	1.3 (4.3)	5,405 (18,386)
Injury with weapon	0 (0)			
Sex offenses, forcible	0 (0)	0 (0)	0 (0)	0(0)
Total costs**	16,469 (30,900)		€19,314 (42,916)	

*MDFT=Multidimensional Family Therapy; CBT=Cognitive Behavioral Therapy; SD=Standard Deviation. *
**The sum of the costs do not exactly equal the total costs because of rounding.

Cost-effectiveness analysis (CEA)

The average quality of life years (QALY's) gained was higher in the MDFT group. The direct medical costs in MDFT were also significantly higher compared to CBT, €3,430 (95% C.I. 1,962–5,196), leading to an ICER of 54,308 Euro per QALY taking a health care perspective. The incremental costs per recovered patient were €43,405. An overview of the costs and effects are shown in Table 8.6. The incremental costs per extra recovered patient were €7,491. We first explored the incremental cost utility from a health care perspective. All of the ICERs (100%) fall in the northeast quadrant of the incremental cost-effectiveness plane, indicating that MDFT is more costly but also more effective than CBT, see Fig. 8.1. When additional costs related to delinquency were included, total costs were not significantly higher in the MDFT group than in the CBT group, €585 (95% C.I. −12,271–11,426), and the ICER increased to 9,266 Euro/QALY, see Table 8.7 (left). Another way to present the uncertainty in the data is the acceptability curve in Fig. 8.2. This curve represents the probability that the ICER is acceptable at different (societal willingness to pay) thresholds. For example, at a threshold of 100,000 Euro/QALY the probability that the ratio is acceptable is around 90%. When including costs for delinquency, the probability that MDFT may be cost effective increases; 56% of the ratios fall into the northeast quadrant and 44% in the southeast quadrant, see Fig. 8.1 (right). When all ratio's fall into the northeast quadrant of the cost-effectiveness plane, it means treatment is more costly and more effective. If all ratio's fall into the south east quadrant, it means treatment is less costly and more effective. Compared to the health care perspective, there is a higher probability that the ratio was acceptable up to a threshold of 65,000 Euro/QALY. However, taking a threshold higher than 65,000 Euro/QALY, the probability that the ICER becomes acceptable is slightly lower when costs for delinquency were included, see Fig. 8.2. This was due to higher uncertainty in the costs when costs related to delinquency were included. Overall, the probability that the ICER is acceptable is higher when costs of delinquency are included.

Table 8.6| Overview costs and incremental effects of adolescents for both groups from a health care perspective

	MDFT*	CBT*
Costs	€5,446 (95% C.I. 4,159 to 7,092)	€2,015 (95% C.I. 1,397 to 2,714)
Incremental effect	0.06 (95% C.I. 0.03 to 0.10)	
ICER	54,308 Euro/QALY	
Incremental costs per recovered patient	€43,405	

*MDFT=Multidimensional Family Therapy; CBT=Cognitive Behavioral Therapy

Table 8.7| Overview costs and incremental effects of adolescents for both groups from a health and criminal justice perspective

	MDFT*	CBT*
Costs	€21,915 (95% C.I. 16,273 to 28,181)	€21,330 (95% C.I. 12,389 to 32,894)
Incremental effect	0.06 (95% C.I. 0.03 to 0.10)	
ICER	9,266 Euro/QALY	
Incremental costs per recovered patient	€7,491	

Fig 8.1|Cost-acceptability planes (left: health care perspective, right: costs of delinquency included)

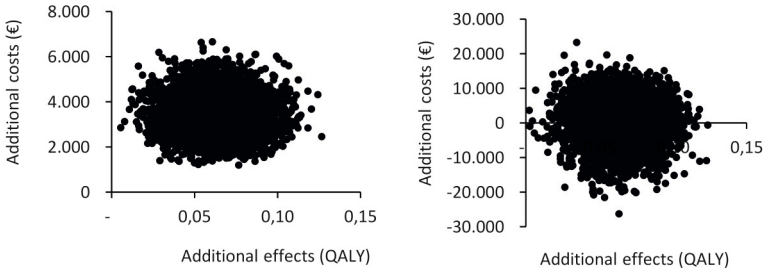
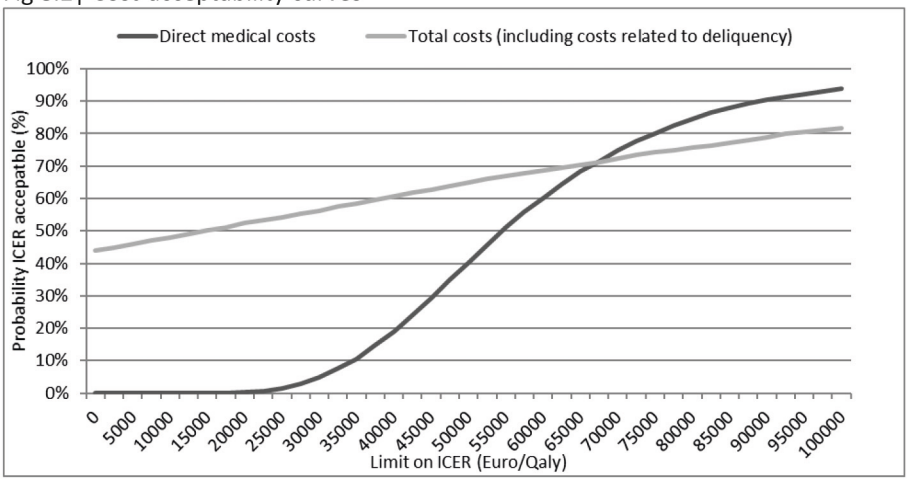


Fig 8.2| Cost-acceptability curves



Sensitivity analysis

A sensitivity analysis was conducted for the traffic offenses, as detailed information to estimate a weighted cost per offense was missing. The SRD did not provide a distinction between offenses that were committed by car or offenses committed by bike (although the difference in costs between these type of offenses is high). Therefore, information from the remarks of the SRD, was assessed to distinguish between these types of offenses. However, these remarks did not always contain this information. Therefore there was much uncertainty around the costs of traffic offenses and a sensitivity analysis was performed, omitting these costs. In addition, there was uncertainty about the probability of getting caught in traffic offenses and subsequently uncertainty in the unit costs. In our sensitivity analysis it was therefore assumed that these costs were zero. After the sensitivity analysis, the incremental costs increased to €4158 (95% C.I. −4664–12873), which lead to an (increased) ICER of 65,823 Euro/QALY.

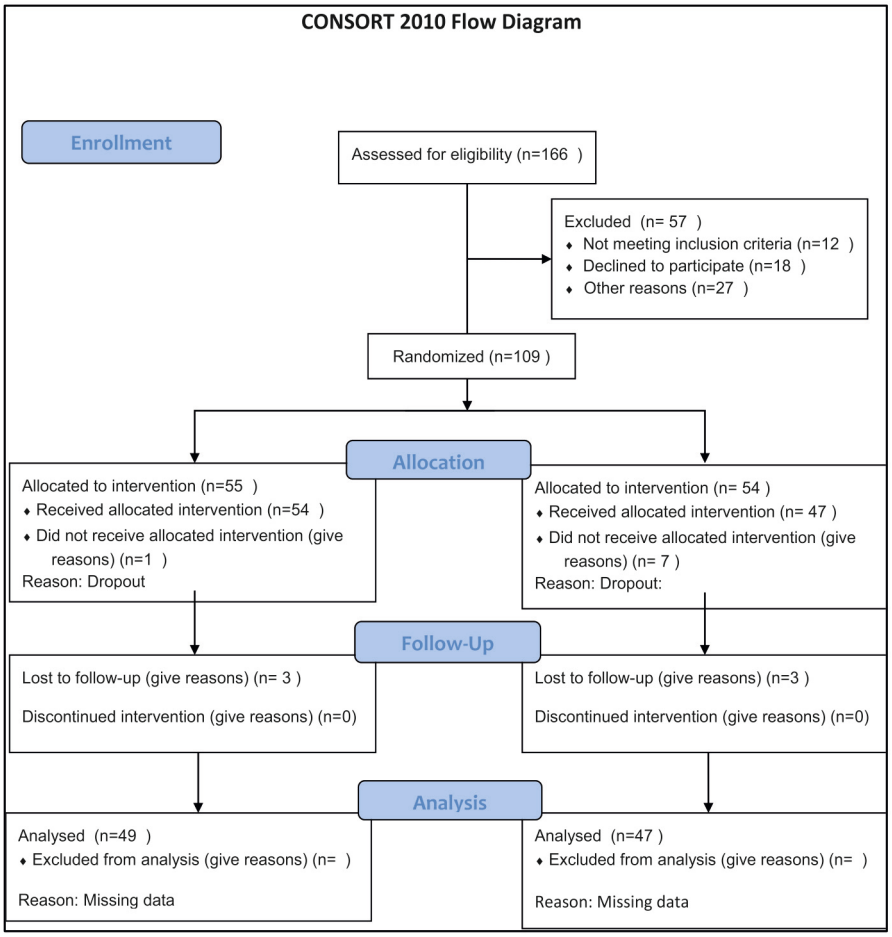
8.4 DISCUSSION

This study is the first cost-effectiveness analysis comparing MDFT to CBT in adolescents with a cannabis use disorder. The higher costs and larger effects in the MDFT group compared to the CBT group resulted in an ICER of 54,308 Euro/QALY and incremental costs per recovered patient of €43,405. This study is also the first to include relevant societal costs − related to delinquency − that go beyond the health care perspective. The results provide a first insight and indicate that inclusion of these costs, affect outcome: including costs related to delinquency resulted in an ICER of 9,266 Euro/QALY and costs per recovered patient of €7,491, as the difference of costs between both treatments decreased. As treatment of adolescents may have a preventive effect on future mental health problems and addiction [34], the ICER may even improve in time. These results underline the importance of adopting a broader perspective regarding cost-effectiveness analysis in mental health care. MDFT was more expensive which is consistent with MDFT being a more intensive treatment than CBT. Overall, health care costs were low in both groups, as adolescents do not have many physical health issues and subsequently do not often make use of health care providers. Only costs of (psychiatric) hospital admissions were high. Regarding the costs related to delinquency, costs of traffic offenses were much larger for MDFT compared to CBT. As there was much uncertainty around the costs for traffic offenses, we performed a sensitivity analysis. As the difference in costs increase, the ICER also increased to 65,823 Euro/QALY. These costs per QALY were still within the range of 80.000,the commonly applied threshold of the Council for Public and Health Care (RVZ). Based on the sources used for estimating the costs related to delinquency, it was not possible to estimate the costs of internet offenses, so we did not include these costs in our analyses. Probably, this does not have a large effect on the results, given that the probability of getting caught for internet offenses is small. Productivity costs were not included in the study because these costs were expected to be negligible as most adolescents (14–19) do not have a day to day job. Although the costs related to delinquency were lower in the MDFT group, the total number of offenses in nearly every category was larger in the MDFT group, compared to the CBT group (i.e., drug offenses, discrimination, destruction, traffic offense, aggression). However, the subcategories show that the CBT group is engaged in more severe and subsequently costly offenses. It is also interesting to note that although the percentage of recovered patients did not significantly differ

between the two treatment groups, we did find a (just) significant effect on quality of life in the MDFT group, compared to the CBT group. Although various clinical outcomes found in the study of [192]were in favor of MDFT, there were no significant effects. Instruments like the Youth Self report [225] are validated and widely used instruments for substance abuse treatment. Although according to the user guide of the EQ-5D [226], this instrument can be used for adolescents, the EQ-5D is not specifically validated for substance abuse treatment yet, and a recent study suggests a small to moderate significant association between clinical effect measures and quality of life for adolescents with persistent major depression, replications are necessary [227]. In this study, quality of life decreased more due to a decrease in pain/discomfort and anxiety/depression. More research is needed to replicate these findings and in general on the usefulness of the EQ-5D in adolescents. Limitations of the randomized controlled trial are extensively discussed in the paper of Hendriks et al. [192]. A first limitation of the present cost-effectiveness study is the relatively short timeframe of 1 year. As substance abuse treatment may prevent future service use and delinquency, it would be interesting to assess future costs and effects. Secondly, outcomes were mostly self-reported. However, we have no reason to expect a bias as this method was used in both treatment groups. Additionally, it was not possible to include subgroup analyses in our study because of a combination of small sample size and skewness. As the study of Hendriks et al. [219] indicated that matching these subgroups to MDFT or CBT may lead to better results (less cannabis use), future cost-effectiveness studies based on these post-hoc analysis should also assess its impact. Thirdly, we only obtained health care costs over three months at 6 and 12 months. These costs were linearly interpolated. However, as the duration of both treatments was 5–6 months, the situation in which the patients were in treatment or not in treatment, was the same during the period of interpolation it seems reasonable to assume that interpolation may not have a significant effect on the results Fourthly, we interpolated our missing utilities. In most cases a sensitivity analysis is needed to determine the impact of these missing values. However, in this case a complete case analysis would have resulted in almost no power in the analysis. Generally, in most studies, the number of missing values increase in time. However, in the present study the amount of missing values at both baseline and at the end of the study were both low, subsequently adding information in our analysis about the value of the missing values in between. The values in between were therefore estimated by using interpolation. As information on baseline and at the end of the

study period was used to estimate these values (in this case utilities), it is believed that the impact of these missing values is low. Fifthly, treatment intensity was not equal between both treatments, as MDFT was much more intensive which may have contributed to the superior effect (quality of life) of MDFT. Finally, although the results suggest that MDFT is more cost-effective than CBT in the Dutch healthcare context where CBT is the standard model of care it may be premature to conclude that these results can be generalized to other settings and contexts. This is a first comprehensive CEA of MDFT compared to CBT and it demonstrated that by including the costs of delinquency the ICERS were modest. The study provides a first insight into the impact of including costs beyond the health care perspective and the importance of adopting a more broad perspective. Future studies should adopt a longer time frame, include costs for delinquency and should also be aimed at subgroups to acquire a more detailed picture of the cost-effectiveness of MDFT versus CBT.

Appendix 8.1 Consort flow diagram



Section/Topic	Item No.	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	162
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	163
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	164
	2b	Specific objectives or hypotheses	164
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	165
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	165
	4b	Settings and locations where the data were collected	165
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	165/166
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	165/166
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	165
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	165
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	165
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	165
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	165
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	n/a
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	167/168
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	168

Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	181
	13b	For each group, losses and exclusions after randomisation, together with reasons	181
Recruitment	14a	Dates defining the periods of recruitment and follow-up	165
	14b	Why the trial ended or was stopped	169
Baseline data	15	A Table showing baseline demographic and clinical characteristics for each group	175
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	168
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	169/170/171
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	172
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	173/174
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	173/174
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	173/174
Other information			
Registration	23	Registration number and name of trial registry	162
Protocol	24	Where the full trial protocol can be accessed, if available	165
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	174

9 DISCUSSION

The high economic and societal burden associated with mental health care problems has evoked a growing interest in distributing mental health care resources more efficiently. In the first place, this thesis focused on identifying patients with personality disorders for the most appropriate setting of care. A decision tool was developed to aid clinicians in referring these patients. In the second place, this thesis focused on collecting evidence about cost-effectiveness of the treatments within the specific settings of care. The treatments considered were collaborative care, i.e. collaboration between settings, and multidimensional family therapy, which is based on collaboration between patient, family members and professionals. The evidence extracted from these evaluations can be used to inform decision makers for the allocation of resources. There were three recurring themes: Allocation of patients, collaboration between settings and interventions based on collaboration.

9.1 PART 1: ALLOCATION OF PATIENTS

The first step in providing cost-effective treatment for patients with mental disorders is a correct referral to the appropriate setting of care. Until now, referral of these patients was often based on implicit expert opinions and less on scientific knowledge. To incorporate scientific knowledge in decision making, in **Chapter 2**, an evidence based decision tool was developed to refer patients with personality disorders to specialized or highly specialized care. The criteria in the tool were based on evidence attained from the literature combined with the input of experts. Therefore, a close cooperation between the researcher and the professionals was needed. The tool was validated and it showed to be sensitive (sensitivity=0.74). The specificity was sufficient (specificity=0.69). This chapter showed that it was possible to develop a validated tool to identify patients in need of specialized and highly specialized care **(Research question 1).**

9.2 PART 2: COLLABORATION BETWEEN SETTINGS

In the second part of this thesis, the cost-effectiveness of specific innovative treatments were investigated. There is evidence of poor collaboration between health care professionals during treatment[228]. The collaborative care model aims

to solve this problem by increasing the collaboration between health care professionals that work in different settings like the care manager, therapist and psychiatrist [23]. It is mostly used to treat Depressive Disorder (MDD) patients in a primary care setting [32]. In this thesis, the cost-effectiveness of collaborative care was evaluated for MDD patients in the primary care setting, that is the family practice, the occupational care and the outpatient general hospital setting and for GAD and PD patients in the family practice setting. The outcomes were mixed and depended on the disorder and the setting **(Research question 2)**. For patients with a MDD **(Chapter 3, Chapter 4, Chapter 5),** collaborative care in the family practice setting might be a promising intervention. Although the incremental cost effectiveness ratio (ICER) was dominant in this setting **(Chapter 4),** the effect subsided after 9 months, when the treatment was no longer provided. In the hospital setting **(Chapter 5)** the ICER was €24,690/QALY and therefore the cost-effectiveness was dependent on the willingness to pay. The willingness to pay, in turn, depends on the severity of the disease with a maximum ICER of 80,000 Euro/QALY[145]. In view of the significant disease burden of the patients, the ICER in this study may be acceptable. There was no difference between collaborative care and care as usual in terms of total remission or the amount of depressive symptoms. However, the number of adverse events did differ between the groups, decreasing more in the collaborative care group, and this may have led to improved quality of life for these patients despite the continued presence of depressive symptoms. In the occupational health setting **(Chapter 3)** the results were less promising and although the costs for collaborative care were lower compared to care as usual, the effects were also slightly lower (not significant). However, for GAD and PD patients in family practice, collaborative care was again a dominant intervention **(Chapter 6)**.

As the patients in most of the collaborative care studies consisted of working adults, productivity costs **(Chapter 3, Chapter 4, Chapter 6)** were included. The impact of inclusion of societal costs on the outcomes was large, especially in the occupational healthcare setting **(Chapter 3)**. The percentage of societal costs out of the total costs (CC+CAU) ranged from 6% in the hospital setting **(Chapter 5)**, 48% for MDD in the family practice setting **(Chapter 4)** to 72% for MDD in the occupational setting **(Chapter 3)**. For GAD and PAD, the productivity costs were 48% **(chapter 6)** out of the total costs. The productivity costs of patients that were treated using the collaborative care model were lower compared to patients in the care as usual group independent of the disorder and setting. Therefore, compared

to the health care perspective, collaborative care was always more cost-effective when a societal perspective was taken. In **Chapter 4** and **Chapter 6**, the inclusion of productivity costs, modified the conclusions as collaborative care turned out to be dominant. Due to the high age of the population in **Chapter 5** only the costs of household work and informal care were relevant.

9.3 PART 3: INTERVENTIONS BASED ON COLLABORATION

Besides collaborative care, other interventions have incorporated collaboration. Family therapy is an example of such an intervention as it involves the patients, the professional and its family during treatment. It is considered an evidence-based practice treatment for children and adolescents with externalizing disorders, symptoms of delinquency and/or substance use disorder [37,38]. There are some studies, evaluating the cost-effectiveness of family therapy, but the quality of these studies is limited and new studies using higher quality standards are necessary **(Chapter 7).** In **Chapter 8**, such a study was conducted by investigating the cost-effectiveness of Multidimensional Family Therapy (MDFT) compared to Cognitive Behavioral Therapy (CBT) for adolescents with externalizing disorders, symptoms of delinquency and/or substance use disorder. This study showed that MDFT was a promising intervention and the ICER was low, namely 9,266 Euro/QALY.

As the intervention group in our study concerned substance abusing adolescents who in general do not work, the societal costs were mainly due to the costs of delinquency. Out of the total costs (MDFT+CBT) 83% consisted of costs for delinquency **(Chapter 8).** Including these cost had a large impact on the outcomes of the study as the ICERS became lower.
Although family therapy seemed to be a cost-effective intervention, additional studies which comply to the quality requirements of economic evaluations are necessary **(Research question 3).**

9.4 LIMITATIONS

Although this thesis has accounted for some important issues on cost-effectiveness in mental health care, there are some limitations which need to be addressed. Firstly, when validating the decision tool, clinical judgment on referral was used as

a golden standard. The clinicians both assessed the decision tool and provided clinical judgment which may have biased the results **(Chapter 2)**. Secondly, all cost-effectiveness studies only considered a time frame of 1 year, so there was uncertainty on the long term effects. Often clinical trials are limited in their time frames by reasons of funding. To overcome this limitation, decision analytic models should be developed, so longer time frames, based on literature can be applied[229]. In **Chapter 4** and **Chapter 8**, the application of such models on our data may have a large influence the outcomes of these studies. In **Chapter 4**, the effect of the intervention diminishes at the end of the study and therefore it is expected that the cost-effectiveness of collaborative care will decrease when future changes are integrated into the analysis. In **Chapter 8**, MDFT is applied to adolescents and therefore the future effectiveness and cost savings may have been underestimated. Hence, a modeling approach should be used additionally to capture these long-term effects.

The innovative interventions described in this thesis were not always applied in the most optimal way and improvements for future research are recommended. Collaborative care in the occupational health setting can be improved by increasing the collaboration between caregivers, so the treatment may become more cost-effective (**Chapter 3**). In case of GAD and PD, collaborative care may be further improved by increasing the case load of care managers, adjusting follow-up procedures to fit into the daily tasks of the care manager and improving medication prescription and adherence by a greater role of the care manager and the psychiatrist in medication management.
Another limitation was the small sample size in two studies (**Chapter 4, Chapter 5**). In **Chapter 4**, the small sample size was caused by the decision to exclude patients that were identified by the general practitioner (GP) in order to avoid selection bias. In **Chapter 5,** the small sample size was expected given the high burden of comorbid illness causing patients being too ill to participate in the study. In this case it turned out that it was not feasible to include more patients. As the burden of these patients is high and understudied, more research is necessary for more appropriate research designs in order to increase inclusion rates of such patients.

In this thesis, all cost-effectiveness studies included both Quality-Adjusted Life Years (QALYs) and productivity losses. In the past, the United States (U.S.) Panel on Cost-effectiveness in Health and Medicine has recommended to incorporate

productivity costs as health effects (e.g. QALY) in the denominator and not in the nominator to avoid double counting [230]. Cost-effectiveness studies conducted in the US followed these guidelines. However, in this thesis we included these costs in the nominator for two reasons. Firstly, other than in the U.S., the Netherlands has an encompassing mix of social security and private insurance systems, and this is expected to compensate for major income reductions due to diseases. As the level of social benefit is high, we expect the effect on income and subsequently on quality of life to be less in the Netherlands than in the U.S. Secondly, it is argued that the patient's viewpoint is useful for measuring quality of life but not for productivity cost [230]. Recently, the Second Panel on Cost Effectiveness in Health and Medicine released updated recommendations and although they still warn for the risk of double counting, they also highlight the importance of including societal costs in cost-effectiveness analysis to estimate the societal impact of an intervention more precisely[231]. Evidence of the large impact on outcomes when including these societal costs was already provided in the study of Krol et al. [18] for patients with a depression. Therefore, in this thesis, a societal perspective was taken for all cost-effectiveness studies. The costs relevant to the population under study were included. In most of the collaborative care studies, productivity costs **(Chapter 3, Chapter 4, Chapter 6)** were incorporated as the population consisted of working adults. Only, in the case of collaborative care in the hospital setting **(Chapter 5)**, these costs were not included. In this study, most patients were older than 60 and did not have a paid job, so only costs of household work and informal care cost were considered to be relevant. In case of MDFT, only the costs of delinquency were determined **(Chapter 8)**. Productivity costs were considered to be less significant as adolescents often do not have full time jobs. In contrast to productivity costs which can be estimated by using the Treatment Inventory Cost in psychiatric patients (TiC-P) instrument[13], there is also no validated questionnaire to assess the costs of delinquency yet. Therefore, the volume of the number of delinquent act were based on a validated tool the SRD[232] and the unit costs for these delinquent acts were estimated in **Chapter 8.** The impact of these costs on the outcomes of this study was even larger compared to the impact of the inclusion of productivity costs in the collaborative care studies. Costs for school absence were not considered in this study. However, these costs may be relevant, as there is evidence of an association between school avoidance and mental illnesses [233]. Hence, future research should focus on measuring and valuing school absenteeism.

The EQ-5D was used in this thesis to value the quality of life. In case of adults, the EQ-5D has been validated and a recent study suggested a small to moderate association between clinical effect measures and quality of life for most common mental disorders[12]. Although the user guide of the EQ-5D[226] indicates that the instrument may also be used for adolescents, the EQ-5D is not validated for this population and except for depressive disorders, no evidence on its sensitivity exists[227]. More research is needed on the validity of the EQ-5D, especially for adolescents.

Recent developments for the EQ-5D may be relevant for the field of mental health care. In order to improve the instruments' sensitivity and to reduce ceiling effects, a new version of the instrument came out in 2009. It comprises the same number of dimensions, but differs on the number of levels (5 instead of 3)[234]. Research, showed that the 5 level EQ-5D outperformed the 3 level EQ-5D on ceiling effects and discriminative power not only for patients in the general population [235], but also for patients with chronic diseases, like depression and personality disorders [236,237]. The reduced ceiling effect of the 3 level EQ-5D will probably be most noticeable in adolescents as they usually are healthy individuals. The research of Ferreira et al. (2016)[238] showed that the new version of the EQ-5D contributed to a significant reduction in the ceiling effect for young adults. However, there are still some methodological issues that need to be addressed, concerning the phrasing of the questions and the high context-dependent responses that indicate a lack of illnesses' experience amongst these adults.

9.5 Clinical recommendations and research implications

The decision tool is already used by clinicians and is intended to be a part of the standard of care of personality disorders in the Netherlands. When the tool is used, it reduces the variation between practices. We assume it will also reduce the number of treatment steps for patients to appropriate cost-effective treatment in a certain setting of care. Future research should evaluate if patients are treated more cost-effective when these decision tools are used compared to patients who are not diagnosed by these tools. There is not always evidence available on the cost-effectiveness and therefore the possible implementation of treatments within those settings. One of the reasons is the lack of funding for research. Another

reason is that many therapists are still opposed by the idea that clinical decisions should also be guided by economic considerations instead of only the needs of the patient[239]. However, in light of the scarcity of resources clinicians should be more open for research on this matter. Cost-utility studies are rare in the field of mental health and the studies on collaborative care and family therapy were the first ones in the Netherlands on this topic. As there is only a limited amount of evidence, more research is necessary. The quality of research should be improved and methodological shortcomings pointed out in this paper should be addressed. The largest improvements are considered to be the use of a societal perspective, studies applying a longer time frame and the use of models to measure uncertainty. The QALY is recommended as the preferred outcome in cost-effectiveness research. The validity of different versions of the EQ-5D for measuring these QALYs is yet to be determined for a wide range of mental disorders. Adolescents should be treated as a subgroup in this kind of research because of the existing ceiling effects.

9.6 Policy implications

Between one-half and two third of the patients in specialized mental health care do not meet the criteria for a psychiatric disorder [240] and may also be treated effectively in primary care. Furthermore, the outcome of the collaborative care trials performed in the context of the Depression initiative[25,26,28,29] showed that treatment can be provided for depressive and anxiety disorders in the primary care setting that is effective as well as cost-effective, in various degrees and depending on the setting, by following the collaborative care model.
Therefore, in 2014, a policy change was introduced in the Netherlands reimbursing GP's, nurse care managers and consultation psychiatrists to provide treatment in the primary care setting for patients with psychological problems without a psychiatric disorder as well as patients with moderately severe, non-complex mental disorders, according to the collaborative care model. This was called "basisGGz ' and 'generalistic GGz'. Only high complex cases were to be referred to specialized mental health care. This has resulted in a growing provision of mental health care within the family practice setting. Therefore, collaborative care models are now part of standard care, allowing the GP to consult medical professionals when needed[240].

9.7 Final remarks

This thesis aimed to add to the ongoing discussions in the field of cost-utility research in mental health care and may have some implications for health policy and future research. The possibility of developing an evidence based tool to refer patients to the appropriate health care setting was showed. This part of the research was innovative in the sense that both evidence from the literature and expert knowledge were combined with innovative methods into a decision tool. This methodology is already improved and is now applied in studies to develop tools for depression and anxiety disorders. When patients are referred to the appropriate setting of care, cost-effective treatment should be applied. This thesis provides indications of the surplus value of incorporating increased collaboration in interventions, however, in light of the limited evidence, replications of these studies are necessary. Overall, the number of high quality cost-effectiveness studies in mental health care is still low and clinicians or decision makers should be aware of the quality and the perspective of the studies when considering a certain treatment.

10 SUMMARY

Mental disorders have a large burden of disease and are the main contributor to chronic conditions for the population of Europe. They are associated with high costs and there is an existing scarcity in resources due to increasing costs and limited budget. Therefore, there is a growing interest in methods to decrease the burden and distribute resources more efficiently. The main purpose of this thesis is to investigate the cost utility of collaboration models from a societal perspective.

In the Netherlands, three healthcare settings exist that identify mental health care patients for appropriate treatment: Primary care, specialized care and highly specialized care. Patients with more severe and complex disorders should be referred to higher intensity settings compared to patients with less severe and complex disorders. Early stratification of more complex and severe patients with evidence based-decision tools for the appropriate setting of care may lead to a reduction in costs and decrease loss of quality of life, as it may reduce the number of treatment steps before effective treatment. In the three settings of care, various treatments may be applied. For policymakers, it is important to have knowledge about the economic consequences and benefits of these treatments. A common type of economic evaluations is a cost-utility analysis (benefits are expressed as quality-adjusted life years (QALYs) and costs are measured by an evidence based instrument). In these evaluations, an innovative treatment is compared to usual care in terms of incremental costs and effects.

The first step in providing cost-effective treatment for patients with mental disorders is to reduce the number of treatment steps for patients to appropriate cost-effective treatment in a certain setting of care. In the first part of this thesis **(Chapter 2)** we address this issue by developing an evidence based decision tool to refer patients with personality disorders to specialized or highly specialized care. The criteria in the tool were based on evidence attained from the literature combined with the input of experts. The tool was validated and it showed to be sensitive (sensitivity=0.74). The specificity was sufficient (specificity=0.69).

In the second and third part **(Chapter 3-6, Chapter 8**) of this thesis the cost-utility of two innovative interventions that both have integrated collaboration, is investigated. The second part **(Chapter 3-6)** contains interventions that are based on the collaboration between settings; the collaborative care model. In these chapters the cost-utility is determined when provided in different settings for two common mental disorders; MDD-and generalized anxiety disorder (GAD) /panic disorders (PD). In **Chapter 3-4** collaborative care for MDD or comorbid MDD in chronically ill patients **(Chapter 5)** is examined by using data of three randomized trials provided in different settings; the occupational setting **(Chapter 3),** the family practice setting **(Chapter 4)**, general hospital setting **(Chapter 5). In Chapter**

6 the cost utility of collaborative care for patients with a GAD and PD in primary care has been studied. The outcomes were mixed and depended on the disorder and the setting. Although the Incremental Cost Effectiveness Ratio (ICER) was dominant in the family practice setting **(Chapter 4),** the effect subsided after 9 months, when the treatment was no longer provided. In the hospital setting **(Chapter 5)** the ICER was €24,690/QALY and therefore the cost-effectiveness was dependent on the willingness to pay. In the occupational health setting **(Chapter 3)** the results were less promising and although the costs for collaborative care were lower compared to care as usual, the effects were also slightly lower. However, for GAD and PD patients in family practice, collaborative care was again a dominant intervention **(Chapter 6).** The results of two of these studies **(Chapter 4, Chapter 6)** depended upon the perspective that was used. When a societal perspective was taken, collaborative care turned out to be dominant

Family therapy is an intervention that has incorporated collaboration by involving the patients, the professional and its family during treatment. **Chapter 7** examines scientific evidence on cost-effectiveness studies for family therapy of externalizing disorders, substance use disorders and delinquency by conducting a systematic review. The number of studies evaluating the cost-effectiveness of family therapy turned out to be limited and new studies using higher quality standards are necessary. In **Chapter 8**, such a study was conducted by investigating the cost-effectiveness of Multidimensional Family Therapy (MDFT) compared to Cognitive Behavioral Therapy (CBT) for adolescents with externalizing disorders, symptoms of delinquency and/or substance use disorder. This study showed that MDFT was a promising intervention, as the ICER was low, namely 9,266 Euro/QALY.

In this thesis we attempted to contribute to the health economics literature in various ways. The decision tool is already used by clinicians and is intended to be a part of the standard of care of personality disorders in the Netherlands. The methodology to develop such an instrument is already improved and is now applied in studies to develop tools for depression and anxiety disorders. For reasons of funding and a less positive attitude towards economic studies cost-utility studies are still rare in the field of mental health. This thesis provides indications of the surplus value of incorporating increased collaboration in interventions, but more high quality research is necessary. Many patients without a psychiatric disorder were unnecessarily treated in the specialized care setting. In that respect it is very promising that collaborative care is already implemented in the Dutch primary care setting. The largest improvements for cost-effectiveness studies are considered to be the use of a societal perspective, studies applying a longer time frame and the use of models to incorporate uncertainty.

11 SAMENVATTING

Psychische stoornissen zijn vaak chronisch van aard en gaan gepaard met een zware ziektelast. Ze worden geassocieerd met hoge kosten. Door de hoge kosten van behandeling en een gelimiteerd budget is er steeds meer interesse in efficiënte behandelingen die de ziektelast verlagen. Het hoofddoel van deze thesis is om de kostenutiliteit van 'collaborative care models' te onderzoeken vanuit een maatschappelijk perspectief.
In Nederland zijn er 3 verschillende lijnen van zorg waarnaar patiënten met psychische stoornissen kunnen worden doorverwezen: eerste lijn zorg, gespecialiseerde zorg en hoog gespecialiseerde zorg. Het is de bedoeling dat patiënten met meer complexe en ernstige stoornissen worden doorverwezen naar meer intensieve zorg dan patiënten die dit in mindere mate hebben. Vroege herkenning van meer complexe en ernstige ziektebeelden kan leiden tot kostenreductie en een vermindering in het verlies van kwaliteit van leven doordat het aantal stappen van (ineffectieve) behandeling wordt gereduceerd. Er zijn verschillende behandelingen die kunnen worden toegepast in de drie lijnen van zorg. Voor beleidsmakers is het van belang om kennis te verkrijgen van de economische consequenties en voordelen van deze behandelingen. Een kostenutiliteitsanalysen kan hieraan bijdragen. Bij een kostenutiliteitsanalysen worden de voordelen uitgedrukt in kwaliteit van leven (QALY) en de kosten worden gemeten door een gevalideerd instrument. Op deze manier wordt een innovatieve behandeling vergeleken met gebruikelijke zorg door een evaluatie van incrementele kosten en effecten.

De eerste stap tot het verkrijgen van kosteneffectieve behandeling is om het aantal stappen om te komen tot zo'n behandeling, te reduceren. In het eerste gedeelte van dit manuscript (Hoofstuk 2) dragen we hieraan bij door een instrument te ontwikkelen om patiënten met persoonlijkheidsstoornissen naar de juiste lijn van zorg te verwijzen; gespecialiseerde zorg of hoog gespecialiseerde zorg De criteria in het instrument zijn gebaseerd op bewijslast uit de literatuur gecombineerd met de input van experts. Het instrument is gevalideerd en het bleek sensitief (sensitiviteit=0,74) en voldoende specifiek (specificiteit=0,69)

In het tweede en derde gedeelte (Hoofdstuk 3-6 en Hoofdstuk 8) van dit proefschrift is de kostenutiliteit onderzocht van twee interventies die gebaseerd zijn op samenwerking. Het tweede gedeelte (Hoofdstuk 3-6) onderzoekt interventies die gebaseerd zijn op samenwerking tussen de verschillende lijnen van zorg; het 'collaborative care model'. In Hoofdstuk 3-6 is de kostenutiliteit van zo'n behandeling in verschillende lijnen geëvalueerd voor twee veelvoorkomende stoornissen, namelijk Major Depressive Disorder (MDD) en Generalized Anxiety Disorder (GAD)/Panic Disorder (PD). In Hoofdstuk 3-4 is 'collaborative care' voor MDD of comorbide MDD in chronisch zieke patiënten (Hoofdstuk 5) onderzocht

door data te gebruiken van 3 gerandomiseerde trials in verschillende lijnen van zorg; de bedrijfsgeneeskundige setting (Hoofdstuk 3), de huisartsensetting (Hoofdstuk 4) en de ziekenhuis setting (Hoofstuk 5). In Hoofdstuk 6 is de kostenutiliteit berekend van 'collaborative care' voor patiënten met GAD en PD in de huisartsensetting. De uitkomsten hingen af van de stoornis en van de lijn van zorg waarin de behandeling plaats vond. Alhoewel de incrementele kosteneffectiviteitsratio (ICER) dominant was in de huisartsensetting (Hoofdstuk 4), nam het effect na het beëindigen van de behandeling (9 maanden) af. In de ziekenhuis setting (Hoofdstuk 5) was er een ICER van €24,690/QALY en was de kosteneffectiviteit afhankelijk van de hoeveelheid die de consument bereid is om te betalen voor 1 QALY. In de bedrijfsgeneeskundige setting (Hoofdstuk 3) waren de resultaten minder hoopvol. Ook al waren de kosten voor 'collaborative care' vergeleken met 'care as usual' lager, de effecten waren tevens lager. Echter voor GAD en PD patiënten in de huisartsensetting was 'collaborative care' weer dominant (Hoofdstuk 6). De resultaten van twee van deze studies (Hoofdstuk 4, Hoofdstuk 6) waren afhankelijk van het perspectief dat gebruikt was. Wanneer een maatschappelijk perspectief werd toegepast, was 'collaborative care' dominant.

Familie therapie is een interventie die samenwerking heeft geïntegreerd in de behandeling door de patiënt, de therapeut en zijn familie in de therapie te betrekken. Hoofdstuk 7 is een systematische review die het wetenschappelijke bewijs voor de kosteneffectiviteit van familie therapie voor externaliserende stoornissen, middelen gebruik en delinquentie beoordeeld. Het bleek dat het aantal studies dat de kosteneffectiviteit van familie therapie evalueert erg beperkt is en er studies nodig zijn met hogere kwaliteitsstandaarden. In Hoofdstuk 8 wordt zo'n studie uitgevoerd door de kosteneffectiviteit van Multidimensionale Familie Therapie (MDFT) te onderzoeken door deze te vergelijken met Cognitieve Gedragstherapie (CBT) voor adolescenten met externaliserende stoornissen, symptomen van delinquentie en/of een middelen stoornis. Deze studie liet zien dat MDFT een veelbelovende interventie was omdat de ICER laag was, namelijk 9,266 Euro/QALY.
In dit proefschrift is een poging gedaan om bij te dragen aan de gezondheid economische literatuur. Het instrument dat we hebben ontwikkeld voor patiënten met een persoonlijkheidsstoornis wordt al gebruikt door clinici en het is de bedoeling dat dit een onderdeel wordt van de standaardzorg in Nederland. De methodologie om zo'n instrument te ontwikkelen is inmiddels verbeterd en wordt nu toegepast in andere studies waarin soortgelijke instrumenten worden ontwikkeld voor depressie en angststoornissen. Door een gelimiteerd budget en een relatief negatieve houding ten opzichte van economische evaluaties, zijn dit soort studies nog steeds een zeldzaamheid in de psychologie. Er zijn aanwijzingen voor de toegevoegde waarde van de integratie van samenwerking in psychologische behandelingen, maar hiervoor is meer onderzoek is nodig. Het is wel duidelijk dat veel patiënten met psychiatrische stoornissen onnodig worden

behandeld in een gespecialiseerde lijn. Het is daarom veelbelovend dat ‘collaborative care’ al is geïmplementeerd in de Nederlandse huisartsensetting. De grootste verbeteringen van de studies in deze thesis ten opzichte van eerdere kosteneffectiviteitsstudies is het gebruik van het maatschappelijk perspectief. De studies kunnen verder nog verbeterd worden door langere time frames en modellen toe te passen.

12 PHD PORTFOLIO

PhD training	
2011	Academic Writing in English, institute of Health, Policy and Management, Erasmus University Rotterdam, The Netherlands
2011	Klaar in 4 jaar, institute of Health, Policy and Management, Erasmus University Rotterdam, The Netherlands
2011	Foundations of Economic Evaluation in Health Care, The University of York, United Kingdom
2011	Advanced Methods for Cost-Effectiveness Analysis: Meeting Decision-Makers' Requirements, The University of York, United Kingdom
2012	Statistical analysis with missing data using multiple imputation and inverse probability weighting, London school of hygiene, United Kingdom
2012	Missing Values in Clinical Research, Netherlands Institute for Health Sciences (NIHES), Rotterdam, the Netherlands
2012	Repeated Measurements, Netherlands Institute for Health Sciences (NIHES), Rotterdam, the Netherlands
2013	Decision analytic modelling methods for economic evaluation, Foundations and Advanced course, University of Glasgow, United Kingdom
2015	Indirect and Mixed Treatment Comparisons, University of Bristol, United Kingdom
Teaching	
2011	Workgroups 'Methoden en Technieken 4', Bachelor Gezondheidswetenschappen, Institute of Health, Policy and Management, Erasmus University Rotterdam, The Netherlands
2012	Workgroups 'Methoden en Technieken 4', Bachelor Gezondheidswetenschappen, Institute of Health, Policy and Management, Erasmus University Rotterdam, The Netherlands
2013	Workgroups 'Methoden en Technieken 4', Bachelor Gezondheidswetenschappen, Institute of Health, Policy and Management, Erasmus University Rotterdam, The Netherlands
2014	Praktijkstage, Bachelor Gezondheidswetenschappen, Institute of Health, Policy and Management, Erasmus University Rotterdam, The Netherlands
Presentations	
2012	Eleventh Workshop on Costs and Assessment in Psychiatry: Mental Health Policy, Economics and Health Care Reforms, The International Center of Mental Health Policy and Economics (ICMPE), Venice, Italy

2013	Twelfth Workshop on Costs and Assessment in Psychiatry - Mental Health Policy and Economics Research: Improving Access, Quality and Outcomes, The International Center of Mental Health Policy and Economics (ICMPE), Venice, Italy
2014	Diagnosis, Prevention and Treatment in Mental Health: Effectiveness and Comparative Effectiveness, The International Center of Mental Health Policy and Economics (ICMPE), Washington, The United States
2015	Jeugd in Onderzoek, Nieuwegein, The Netherlands
Poster presentations	
2011	ISPOR 14th Annual European Congress, Madrid,Spain
2013	Nederlandse Vereniging voor Psychiatrie (NVvP) voorjaarscongres, Maastricht, The Netherlands
2014	ISPOR 17th Annual European Congress, Amsterdam, The Netherlands
2014	Diagnosis, Prevention and Treatment in Mental Health: Effectiveness and Comparative Effectiveness, The International Center of Mental Health Policy and Economics (ICMPE), Washington, The United States
Other congresses	
2011	3nd Lowlands Health Economists' Study Group. (2011). Soesterberg, The Netherlands.
Scientific Publications	
Goorden M, Willemsen, EMC, Bouwmans CAM, Busschbach JJV, Noom MJ, van der Feltz-Cornelis CM, Uyl-de Groot CA, Hakkaart-van Roijen L (2017). Developing a decision tool to identify patients with personality disorders in need of highly specialized care. BMC Psychiatry, 17:317	
Goorden M, Vlasveld MC, Anema JR, van Mechelen W, Beekman ATF, Hoedeman R, van der Feltz-Cornelis CM, Hakkaart-van Roijen L (2014). Cost utility analysis of a collaborative care intervention for major depressive disorder in an occupational healthcare setting. Journal of Occupational Rehabilitation, 24(3): 555-562	
Goorden M, Huijbregts KML, van Marwijk HWJ., Beekman ATF, van der Feltz-Cornelis CM, Hakkaart-van Roijen L (2015). Cost-utility of collaborative care for major depressive disorder in primary care in the Netherlands. Journal of Psychomatic Research, 79(4): 316-23	
Goorden M., van der Feltz-Cornelis CM, van Steenbergen-Weijenburg KM, Horn EK, Beekman ATF, Hakkaart-van Roijen L (2015). Cost-utility of collaborative care for the treatment of comorbid major depressive disorder in outpatients with chronic physical conditions. A randomized controlled trial in the general hospital setting (CC-DIM). Neuropsychiatric Disease and Treatment 13:1881-1893.	
Goorden M., Muntingh ADT , van Marwijk HWJ, Spinhoven P, Adèr HJ, van Balkom , AJLM, van der Feltz-Cornelis CM, Hakkaart-van Roijen L (2015).	

Cost utility analysis of a collaborative stepped care intervention for panic and generalized anxiety disorders in primary care. Journal of Psychomatic Research, 77(1): 57-63.

Goorden M., Schee van der E., Hendriks VM, Hakkaart-van Roijen L (2016). Cost-effectiveness of multidimensional family therapy compared to cognitive behavioral therapy for adolescents with a cannabis use disorder: Data from a randomized controlled trial. Drug and Alcohol Dependence, 162: 154-161.

Goorden M, Schawo SJ, Bouwmans-Frijters CA, Schee van der E, Hendriks VM, Hakkaart-van Roijen L (2016). The cost-effectiveness of family/family-based therapy for treatment of externalizing disorders, substance use disorders and delinquency: a systematic review. BMC Psychiatry, 16: 237

Romijn, G, Riper H., Kok R., Donker T., Goorden M, van Roijen LH, Kooistra L , van Balkom A, Koning J (2015) Cost-effectiveness of blended vs. face-to-face cognitive behavioural therapy for severe anxiety disorders: study protocol of a randomized controlled trial. BMC Psychiatry, 12: 15:311

Horn EK, Verheul, R, Thunnissen, M, Delimon, J, Goorden, M., Hakkaart-van Roijen, L, Soons M, Meerman AM, Ziegler UM, Rossum BV, Stijnen T., Emmelkamp, PM, Busschbach JJ (2016). Cost-Effectiveness of Short-Term Inpatient Psychotherapy Based on Transactional Analysis in Patients With Personality Disorder. Journal of Personality disorders, 30(4):483-501

van Krugten FCW, Kaddouri M, Goorden M, van Balkom AJ, Bockting C., Peeters FP, Hakkaart-van Roijen L (2017). Indicators of patients with major depressive disorder in need of highly specialized care: A systematic review. PLoS One,12(2):e0171659.

van Krugten FCW, Goorden M, van Balkom AJLM, Spijker J, Brouwer WBF, Hakkaart-van Roijen L, Decision Tool Unipolar Depression Consortium (2018). Indicators to facilitate the early identification of patients with major depressive disorder in need of highly specialized care: A concept mapping study. Depression and anxiety, 35(4): 346-352

13 ABOUT THE AUTHOR

Maartje Goorden was born in Sittard on June 3th 1981. She obtained her Master's degree in Psychology at the Erasmus University in Rotterdam in 2008 and her Bachelor in physics at the Utrecht university in 2009. After her master, she first started working in the field of psychology where she collaborated in developing treatment guidelines for patients who are chronically traumatized. She started her PhD at the institute of Health Policy and Management (iBMG) in 2011. The focus of her research was on the cost-effectiveness of treatments in mental health care. Her main interests are health economics, physics, modelling and mathematics . Since 2017 she works as a statistical researcher for the Dutch Central Bureau of Statistics.

14 DANKWOORD

Met veel plezier kijk ik terug op de jaren die ik heb gewerkt bij het instituut Beleid en Management voor de Gezondheidszorg (iBMG). Dit was vooral te danken aan de gezellige collega's die ervoor zorgde dat ik altijd met plezier naar de universiteit ging en me steun gaven wanneer het even tegen zat.

In het speciaal wil ik mijn supervisor Leona bedanken (!); jij hebt me de ruimte gegeven om mij verder te ontwikkelen en wanneer ik de oplossing even niet zag, had jij door je ervaring op het GGz gebied vlak altijd een antwoord paraat en overzag je het proces. De positiviteit die je altijd uitstraalde en het vertrouwen dat je in mij had, heeft me veel geholpen tijdens deze periode. Ik mis nu nog de gezelligheid en gesprekken; bedankt voor al je hulp en de begeleiding! Verder wil ik mijn promotoren Carin en Christina bedanken voor de kennis die jullie hebben gedeeld op respectievelijk het gebied van kosteneffectiviteit en collaborative care, de begeleiding en de kritische opmerkingen die hebben bijgedragen aan de tot stand komen van dit proefschrift.

Ten aanzien van de decision tool persoonlijkheidsstoornissen wil ik graag de clinici bedanken die hebben bijgedragen aan het tot stand komen van dit instrument. In het bijzonder wil ik daarbij Annemieke, Ellen (Willemsen), Jan, Marc en Ellen (Mogendorff) bedanken; het waren altijd constructieve vergaderingen en ik ben blij met ons eindresultaat. Clazien ook bedankt voor jouw grote rol hierin en daarnaast ook de gezelligheid. Annemieke, dank voor je goede voorzitterschap en Ellen, fijn dat ik je ook altijd buiten deze vergaderingen even kon bereiken voor je klinische blik.

Ook wil ik de co-auteurs van mijn artikelen over collaborative care en MDFT bedanken; in het bijzonder Klaas, Anne en Moniek voor jullie inbreng bij de artikelen van collaborative care; fijn dat we altijd even konden overleggen. Saskia, dank voor de goede samenwerking tijdens review van MDFT. Evelien en Vincent dank voor de kritische blik bij het artikel over MDFT.

De leden van de promotiecommissie wil ik bij deze bedanken voor het lezen en beoordelen van mijn proefschrift.

Op een meer persoonlijk vlak wil ik al mijn collega's bij iBMG bedanken voor de gezellige tijd en de lunches. Melinde en Ellen, mijn ex-kamergenootjes, met jullie heb ik een geweldige tijd gehad toen we allemaal nog maar net begonnen en alles nog zo nieuw was. Ik heb veel steun aan jullie gehad en het was fijn om alles te bespreken waar we tegenaan liepen. Maria, I still miss our conversations, the

burgers, squash and of course Jack…;) Mijn ‘nieuwere kamergenoten’ Naomi, Remziye en later nog Esther, Frederique, Marscha en Brenda, dank jullie allemaal voor de fijne tijd.
Mijn vrienden en vriendinnen wil ik bedanken; In het bijzonder Roos, en hoe kunnen we hem vergeten, Ygor. Als laatste wil ik mijn ouders, familie, vrienden, Gerard en mijn kleine mannetjes Tygo en Maxim bedanken. Dank voor alle afleiding/steun die jullie me hebben gegeven.

15 REFERENCES

1. Wittchen HU, Jacobi F, Rehm J, et al. The size and burden of mental disorders and other disorders of the brain in europe 2010. Eur Neuropsychopharmacol. 2011;21(9):655-679.

2. Stein DJ, Lund C, Nesse RM. Classification systems in psychiatry: Diagnosis and global mental health in the era of DSM-5 and ICD-11. Curr Opin Psychiatry. 2013;26(5):493-497.

3. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: A systematic analysis for the global burden of disease study 2010. Lancet. 2012;380(9859):2197-2223.

4. World health organization. Global health estimates 2014 summary tables. http://www.who.int/healthinfo/global_burden_disease/en/. Updated 2014. Accessed 10/2016, 2016.

5. Smit F, Cuijpers P, Oostenbrink J, Batelaan N, de Graaf R, Beekman A. Costs of nine common mental disorders: Implications for curative and preventive psychiatry. J Ment Health Policy Econ. 2006;9(4):193-200.

6. Perlis RH. A clinical risk stratification tool for predicting treatment resistance in major depressive disorder. Biol Psychiatry. 2013;74(1):7-14.

7. Wang PS, Aguilar-Gaxiola S, Alonso J, et al. Worldwide use of mental health services for anxiety, mood, and substance disorders: Results from 17 countries in the WHO world mental health (WMH) surveys. Lancet. 2007;370(9590):841-850.

8. Starfield B, Shi L, Macinko J. Contribution of primary care to health systems and health. Milbank Q. 2005;83(3):457-502.

9. van Krugten FC, Kaddouri M, Goorden M, et al. Indicators of patients with major depressive disorder in need of highly specialized care: A systematic review. PLoS One. 2017;12(2):e0171659.

10. Cheung K, Oemar M, Oppe M, Rabin R. Eq-5D user guide, basic information on how to use EQ-5D. 2009.

11. Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. BMJ. 1990;300:230-235.

12. Mulhern B, Mukuria C, Barkham M, et al. Using generic preference-based measures in mental health: Psychometric validity of the EQ-5D and SF-6D. Br J Psychiatry. 2014;205(3):236-243.

13. Bouwmans C, de Jong K, Timman R, et al. Feasibility, reliability and validity of a questionnaire on health care consumption and productivity loss in patients with a psychiatric disorder (TiC-P). BMC Health Services Research. 2013;13:217.

14. Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. J Health Econ. 1995;14(2):171-189.

15. Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, Kanters T, Tan SS. Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. 2015.

16. Zorginstituut Nederland. Richtlijn voor het uitvoeren van economische evaluaties. https://www.ispor.org/PEguidelines/source/NL-Economic_Evaluation_Guidelines.pdf. Updated 2016. Accessed January, 2016.

17. De Graaf R, Tuithof M, Van Dorsselaer S, Ten Have M. Verzuim door psychische en somatische aandoeningen bij werkenden: Resultaten van de 'netherlands mental health survey and incidence study-2 (NEMESIS-2). 2011.

18. Krol M, Papenburg J, Koopmanschap M, Brouwer W. Do productivity costs matter?: The impact of including productivity costs on the incremental costs of interventions targeted at depressive disorders. Pharmacoeconomics. 2011;29(7):601-619.

19. Stone PW, Chapman RH, Sandberg EA, Liljas B, Neumann PJ. Measuring costs in cost-utility analyses. variations in the literature. Int J Technol Assess Health Care. 2000;16(1):111-124.

20. Knapp M, McDaid D, Evers S, MHEEN group. Cost-effectiveness and mental health; MHEEN II policy briefing. 2008.

21. Pampallona S, Bollini P, Tibaldi G, Kupelnick B, Munizza C. Combined pharmacotherapy and psychological treatment for depression: A systematic review. Arch Gen Psychiatry. 2004;61(7):714-719.

22. McHugh RK, Whitton SW, Peckham AD, Welge JA, Otto MW. Patient preference for psychological vs pharmacologic treatment of psychiatric disorders: A meta-analytic review. J Clin Psychiatry. 2013;74(6):595-602.

23. Van der Feltz-Cornelis CM. The depression initiative. description of a collaborative care model for depression in the primary care setting in the netherlands. Clinical Neuropsychiatry. 2011;8(4):260-267.

24. Vlasveld MC, van der Feltz-Cornelis CM, Ader HJ, et al. Collaborative care for major depressive disorder in an occupational healthcare setting. Br J Psychiatry. 2012;200(6):510-511.

25. Steenbergen-Weijenburg K.M., van der Feltz-Cornelis C.M., van Benthem T.B., et al. Efficacy of collaborative care for comorbid major depressive disorder in chronic medically ill patients in the general hospital outpatient setting. A multi center RCT in the netherlands depression initiative. tijdschr Psychiatr. 2015;57(4):248-257.

26. Huijbregts KML, de Jong FJ, Marwijk HWJ, et al. A target-driven collaborative care model for major depressive disorder is effective in primary care in the netherlands. A randomised clinical trial from the depression initiative. Journal of Affective disorders. 2013;146(3):328-337.

27. de Jong FJ, van Steenbergen-Weijenburg KM, Huijbregts KM, et al. The depression initiative. description of a collaborative care model for depression and of the factors influencing its implementation in the primary care setting in the netherlands. Int J Integr Care. 2009;9:e81.

28. Muntingh ADT, van der Feltz-Cornelis CM, van Marwijk HWJ, et al. Effectiveness of collaborative stepped care for anxiety disorders in primary care: A pragmatic cluster randomized controlled trial. Arch Gen Psychiatry. 2013;83:37-44.

29. Vlasveld MC, van der Feltz-Cornelis CM, Ader HJ, et al. Collaborative care for sick-listed workers with major depressive disorder: A randomised controlled trial from the netherlands depression initiative aimed at return to work and depressive symptoms. Occup Environ Med. 2013;70(4):223-230.

30. Green C, Richards DA, Hill JJ, et al. Cost-effectiveness of collaborative care for depression in UK primary care: Economic evaluation of a randomised controlled trial (CADET). PLoS One. 2014;9(8):e104225.

31. Jacob V, Chattopadhyay SK, Sipe TA, et al. Economics of collaborative care for management of depressive disorders: A community guide systematic review. Am J Prev Med. 2012;42(5):539-549.

32. van Steenbergen-Weijenburg KM, van der Feltz-Cornelis CM, Horn EK, et al. Cost-effectiveness of collaborative care for the treatment of major depressive disorder in primary care. A systematic review. BMC Health Serv Res. 2010;10:19.

33. Liddle HA. Multidimensional Family Therapy for Adolescent Cannabis users, Cannabis Youth Treatment (CYT) Series, 2002;5.

34. Liddle HA, Rowe CL, Dakof GA, Ungaro RA, Henderson ZE. Early intervention for adolescent substance abuse: Pretreatment to posttreatment outcomes of a randomized clinical trial comparing multidimensional family therapy and peer group treatment. J Psychoactive Drugs. 2004;36(1):49-63.

35. Henggeler SW, Borduin CM. Family therapy and beyond: A multisystemic approach to treating the behaviour problems of children and adolescents. Pacific Grove: CA: Brooks/Cole; 1990.
36. Alexander JF, Parsons BV. Functional family therapy. Monthery: CA: Brooks/Cole; 1982.

37. von Sydow K, Retzlaff R, Beher S, Haun MW, Schweitzer J. The efficacy of systemic therapy for childhood and adolescent externalizing disorders: A systematic review of 47 RCT. Family Process. 2013;52(4):576-618.

38. Baldwin SA, Christian S, Berkeljon A, Shadish WR. The effects of family therapies for adolescent delinquency and substance abuse: A meta-analysis. J Marital Fam Ther. 2012;38(1):281-304.

39. Lenzenweger MF. Epidemiology of personality disorders. Psychiatr Clin North Am. 2008;31(3):395-403, vi.

40. Soeteman DI, Hakkaart-van Roijen L, Verheul R, Busschbach JJ. The economic burden of personality disorders in mental health care. J Clin Psychiatry. 2008;69(2):259-265.

41. Skodol AE, Gunderson JG, McGlashan TH, et al. Functional impairment in patients with schizotypal, borderline, avoidant, or obsessive-compulsive personality disorder. Am J Psychiatry. 2002;159(2):276-283.

42. Bender DS, Dolan RT, Skodol AE, et al. Treatment utilization by patients with personality disorders. Am J Psychiatry. 2001;158(2):295-302.

43. Moran P, Rendu A, Jenkins R, Tylee A, Mann A. The impact of personality disorder in UK primary care: A 1-year follow-up of attenders. Psychol Med. 2001;31(8):1447-1454.

44. Bateman A, Fonagy P. Health service utilization costs for borderline personality disorder patients treated with psychoanalytically oriented partial hospitalization versus general psychiatric care. Am J Psychiatry. 2003;160(1):169-171.

45. Tyrer P. The problem of severity in the classification of personality disorder. J Pers Disord. 2005;19(3):309-314.

46. Tyrer P, Reed GM, Crawford MJ. Classification, assessment, prevalence, and effect of personality disorder. Lancet. 2015;385(9969):717-726.

47. Soeteman DI, Timman R, Trijsburg RW, Verheul R, Busschbach JJ. Assessment of the burden of disease among inpatients in specialized units that provide psychotherapy. Psychiatr Serv. 2005;56(9):1153-1155.

48. Sobocki P, Ekman M, Agren H, et al. Health-related quality of life measured with EQ-5D in patients treated for depression in primary care. Value Health. 2007;10(2):153-160.

49. Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ. Multidisciplinaire richtlijn persoonlijkheidsstoornissen. 2008;AF0806:1-208.

50. Crawford MJ, Koldobsky N, Mulder R, Tyrer P. Classifying personality disorder according to severity. J Pers Disord. 2011;25(3):321-330.

51. Kane M, &, Trochim W. Concept mapping for planning and evaluation. California: Sage publications, Inc; 2006.

52. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ. 2009;339:b2700.

53. Concept systems incorporated, ed. The concept system CS global software guide version 4.0. 4th ed. New York: ; 2011. www.conceptsystems.com.

54. Trochim W. An introduction to concept mapping for planning and evaluation. Eval Program Plann. 1989;12(1):1-16.

55. Barnicot K, Katsakou C, Marougka S, Priebe S. Treatment completion in psychotherapy for borderline personality disorder: A systematic review and meta-analysis. Acta Psychiatr Scand. 2011;123(5):327-338.

56. Barnow S, Arens EA, Sieswerda S, Dinu-Biringer R, Spitzer C, Lang S. Borderline personality disorder and psychosis: A review. Curr Psychiatry Rep. 2010;12(3):186-195.

57. Chiesa M, Sharp R, Fonagy P. Clinical associations of deliberate self-injury and its impact on the outcome of community-based and long-term inpatient treatment for personality disorder. Psychother Psychosom. 2011;80(2):100-109.

58. Goodman G, Hull JW, Clarkin JF, Yeomans FE. Comorbid mood disorders as modifiers of treatment response among inpatients with borderline personality disorder. J Nerv Ment Dis. 1998;186(10):616-622.

59. Gunderson JG, Daversa MT, Grilo CM, et al. Predictors of 2-year outcome for patients with borderline personality disorder. Am J Psychiatry. 2006;163(5):822-826.

60. Gunderson JG, Stout RL, McGlashan TH, et al. Ten-year course of borderline personality disorder: Psychopathology and function from the collaborative longitudinal personality disorders study. Arch Gen Psychiatry. 2011;68(8):827-837.

61. McMurran M, Huband N, Overton E. Non-completion of personality disorder treatments: A systematic review of correlates, consequences, and interventions. Clin Psychol Rev. 2010;30(3):277-287.

62. Ryle A, Golynkina K. Effectiveness of time-limited cognitive analytic therapy of borderline personality disorder: Factors associated with outcome. Br J Med Psychol. 2000;73 (Pt 2):197-210.

63. Skodol AE, Siever LJ, Livesley WJ, Gunderson JG, Pfohl B, Widiger TA. The borderline diagnosis II: Biology, genetics, and clinical course. Biol Psychiatry. 2002;51(12):951-963.

64. Thormählen B, Weinryb RM, Norén K, Vinnars B, Bågedahl-Strindlund M. Patient factors predicting dropout from supportive-expressive psychotherapy for patients with personality disorders. Psychother Res. 2003;13(4).

65. Yen S, Shea MT, Battle CL, et al. Traumatic exposure and posttraumatic stress disorder in borderline, schizotypal, avoidant, and obsessive-compulsive personality disorders: Findings from the collaborative longitudinal personality disorders study. J Nerv Ment Dis. 2002;190(8):510-518.

66. Yoshida K, Tonai E, Nagai H, et al. Long-term follow-up study of borderline patients in japan: A preliminary study. Compr Psychiatry. 2006;47(5):426-432.

67. van Manen JG, Kamphuis JH, Goossensen A, Timman R, Busschbach JJ, Verheul R. In search of patient characteristics that may guide empirically based treatment selection for personality disorder patients-a concept map approach. J Pers Disord. 2012;26(4):481-497.

68. Bedi RP. Concept mapping the client's perspective on counseling alliance formation. J couns psychol. 2006;53(1):26-35.

69. Stoffers JM, Vollm BA, Rucker G, Timmer A, Huband N, Lieb K. Psychological therapies for people with borderline personality disorder. Cochrane Database Syst Rev. 2012;8:CD005652.
70. Newton-Howes G, Clark LA, Chanen A. Personality disorder across the life course. Lancet. 2015;385(9969):727-734.

71. Ward JH. Hierachical grouping to optimize an objective function. J Am Statist Assoc. 1963;58:236-244.

72. van 't Land H, Schoemaker C, eds. Trimbos zakboek psychische stoornissen. 2nd ed. Utrecht: Uitgeverij de Tijdstroom; 2008.

73. Anema JR, Jettinghoff K, Houtman I, Schoemaker CG, Buijs PC, van den Berg R. Medical care of employees long-term sick listed due to mental health problems: A cohort study to describe and compare the care of the occupational physician and the general practitioner. J Occup Rehabil. 2006;16(1):41-52.

74. Gilbody S, Bower P, Torgerson D, Richards D. Cluster randomized trials produced similar results to individually randomized trials in a meta-analysis of enhanced care for depression. J Clin Epidemiol. 2008;61(2):160-168.

75. van der Feltz-Cornelis CM, Hoedeman R, de Jong FJ, et al. Faster return to work after psychiatric consultation for sicklisted employees with common mental disorders compared to care as usual. A randomized clinical trial. Neuropsychiatr Dis Treat. 2010;6:375-385.

76. Bower P, Gilbody S. Stepped care in psychological therapies: Access, effectiveness and efficiency. narrative literature review. Br J Psychiatry. 2005;186:11-17.

77. Vlasveld MC, van der Feltz-Cornelis CM, Adèr HJ, et al. Collaborative care for sick-listed workers with major depressive disorder: a randomised controlled trial from the Netherlands Depression Initiative aimed at return to work and depressive symptoms.OEM.2012;70(4):223-230.

78. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606-613.

79. van Vliet IM, Leroy H, van Megen HJM. De MINI-internationaal neuropsychiatrisch interview: Een kort gestructureerd diagnostisch interview voor DSM-IV en ICD-10 psychiatrische stoornissen. Tijdschrift voor psychiatrie. 2007;49.

80. Vlasveld MC, Anema JR, Beekman AT, et al. Multidisciplinary collaborative care for depressive disorder in the occupational health setting: Design of a randomised controlled trial and cost-effectiveness study. BMC Health Serv Res. 2008;8:99.

81. van der Feltz-Cornelis CM. Towards integrated primary health care for depressive disorder in the netherlands. the depression initiative. Int J Integr Care. 2009;9:e83.

82. mynors-wallis L. Problem-solving treatment for anxiety and depression. A practical guide. Oxford: Oxford University Press; 2005.

83. Doppegieter RMS, Willems JHBM. Code gegevensverkeer en samenwerking bij arbeidsverzuim en reïntegratie. Utrecht: KNMG; 2006.

84. Van de klink JJL, Ausems CMM, Beijderwellen BD, et al. Handelen van de bedrijfsarts bij werkenden met psychische problemen. Utrecht: NVAB; 2007.

85. Hakkaart-van Roijen L. Manual Trimbos/iMTA questionnaire for costs associated with psychiatric illness (in dutch). J Consult Clin Psychol. 2002;59(1):12-19.
86. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. Handleiding voor kostenonderzoek: Methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. 2010.

87. van Roijen L, Essink-Bot ML, Koopmanschap MA, Bonsel G, Rutten FF. Labor and health status in economic evaluation of health care. the health and labor questionnaire. Int J Technol Assess Health Care. 1996;12:405-415.

88. IBM Corp. Released 2010. IBM SPSS statistics for windows, version 19.0. 2010.
89. Box GEP, Cox DR. An analysis of transformations. Journal of the Royal Statistical Society. 1964;26:211-234.

90. Blonk RWB, Brenninkmeijer V, Lagerveld SE, Houtman ILD. Return to work: A comparison of two cognitive behavioural interventions in cases of work-related psychological complaints among the self-employed Work & Stress. 2006;20(2):129-144.

91. Adler DA, McLaughlin TJ, Rogers WH, Chang H, Lapitsky L, Lerner D. Job performance deficits due to depression. Am J Psychiatry. 2006;163(9):1569-1576.

92. van der Klink JJ, Blonk RW, Schene AH, van Dijk FJ. Reducing long term sickness absence by an activating intervention in adjustment disorders: A cluster randomised controlled design. Occup Environ Med. 2003;60(6):429-437.

93. Schene AH, Koeter MW, Kikkert MJ, Swinkels JA, McCrone P. Adjuvant occupational therapy for work-related major depression works: Randomized trial including economic evaluation. Psychol Med. 2007;37(3):351-362.

94. World Health Organization. Towards a common language for functioning, disability and health: 2002.

95. Loisel P, Durand M, Berhelette D, et al. Disability prevention-new paradigm for the management of occupational back pain. Dis Manage Health Outcomes. 2001;9(7):351-360.

96. Lagerveld SE, Bultmann U, Franche RL, et al. Factors associated with work participation and work functioning in depressed workers: A systematic review. J Occup Rehabil. 2010;20(3):275-292.

97. Dekkers-Sanchez PM, Hoving JL, Sluiter JK, Frings-Dresen MH. Factors associated with long-term sick leave in sick-listed employees: A systematic review. Occup Environ Med. 2008;65(3):153-157.

98. Organisation for economic cooperation and development (OECD). Sick on the job? myths and realities about mental health and work. Paris: OECD publishing; 2012.

99. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3(11):e442.

100. Bower P, Gilbody S, Richards D, Fletcher J, Sutton A. Collaborative care for depression in primary care. making sense of a complex intervention: Systematic review and meta-regression. Br J Psychiatry. 2006;189:484-493.

101. Miller CJ, Grogan-Kaylor A, Perron BE, Kilbourne AM, Woltmann E, Bauer MS. Collaborative chronic care models for mental health conditions: Cumulative meta-analysis and metaregression to guide future research and implementation. Med Care. 2013;51(10):922-930.

102. Woltmann E, Grogan-Kaylor A, Perron B, Georges H, Kilbourne AM, Bauer MS. Comparative effectiveness of collaborative chronic care models for mental health conditions across primary, specialty, and behavioral health care settings: Systematic review and meta-analysis. Am J Psychiatry. 2012;169(8):790-804.

103. Archer J, Bower P, Gilbody S, et al. Collaborative care for depression and anxiety problems. Cochrane Database Syst Rev. 2012;10:CD006525.

104. Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on health economic criteria. Int J Technol Assess Health Care. 2005;21(2):240-245.

105. Aragones E, Lopez-Cortacans G, Sanchez-Iriso E, et al. Cost-effectiveness analysis of a collaborative care programme for depression in primary care. J Affect Disord. 2014;159:85-93.

106. Karssen B, Schipper M, Jurling B. Praktijkkosten en opbrengsten van huisartsenpraktijken, eindrapportages van een onderzoek naar de praktijkkosten en opbrengsten van huisartsenpraktijken in nederland in 2006: Definitief rapport. 2009.

107. Hingstman L, Kenens RJ. Cijfers uit de registratie van huisartsen: Peiling 2010. 2010.
108. Boerma WG, van der Zee J, Fleming DM. Service profiles of general practitioners in europe. european GP task profile study. Br J Gen Pract. 1997;47(421):481-486.

109. Prins M, Bosmans J, Verhaak P, et al. The costs of guideline-concordant care and of care according to patients' needs in anxiety and depression. J Eval Clin Pract. 2011;17(4):537-546.

110. Smolders M, Laurant M, Verhaak P, et al. Which physician and practice characteristics are associated with adherence to evidence-based guidelines for depressive and anxiety disorders? Med Care. 2010;48(3):240-248.

111. IJff MA, Huijbregts KM, van Marwijk HW, et al. Cost-effectiveness of collaborative care including PST and an antidepressant treatment algorithm for the treatment of major depressive disorder in primary care; a randomised clinical trial. BMC Health Serv Res. 2007;7:34.

112. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. primary care evaluation of mental disorders. patient health questionnaire. JAMA. 1999;282(18):1737-1744.

113. Lamers LM, Stalmeier PF, McDonnell J, Krabbe PF, van Busschbach JJ. Measuring the quality of life in economic evaluations: The dutch EQ-5D tariff. Ned Tijdschr Geneeskd. 2005;149(28):1574-1578.

114. Unutzer J, Katon W, Williams JW,Jr, et al. Improving primary care for depression in late life: The design of a multicenter randomized trial. Med Care. 2001;39(8):785-799.

115. World Health Organization. The global burden of disease: 2004 update. 2008.

116. Katon WJ. Epidemiology and treatment of depression in patients with chronic medical illness. Dialogues Clin Neurosci. 2011;13(1):7-23.

117. Egede LE. Major depression in individuals with chronic medical disorders: Prevalence, correlates and association with health resource utilization, lost productivity and functional disability. Gen Hosp Psychiatry. 2007;29(5):409-416.

118. Van der Feltz-Cornelis CM, Ten Have M, Penninx BW, Beekman AT, Smit JH, De Graaf R. Presence of comorbid somatic disorders among patients referred to mental health care in the netherlands. Psychiatr Serv. 2010;61(11):1119-1125.

119. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: Meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med. 2000;160(14):2101-2107.

120. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: Results from the world health surveys. Lancet. 2007;370(9590):851-858.

121. Simon GE. Social and economic burden of mood disorders. Biol Psychiatry. 2003;54(3):208-215.

122. Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. Gen Hosp Psychiatry. 2007;29(2):147-155.

123. Neumeyer-Gromen A, Lampert T, Stark K, Kallischnigg G. Disease management programs for depression: A systematic review and meta-analysis of randomized controlled trials. Med Care. 2004;42(12):1211-1221.

124. Gilbody S, Bower P, Fletcher J, Richards D, Sutton AJ. Collaborative care for depression: A cumulative meta-analysis and review of longer-term outcomes. Arch Intern Med. 2006;166(21):2314-2321.

125. Unutzer J, Katon W, Callahan CM, et al. Collaborative care management of late-life depression in the primary care setting: A randomized controlled trial. JAMA. 2002;288(22):2836-2845.

126. Richards DA, Lovell K, Gilbody S, et al. Collaborative care for depression in UK primary care: A randomized controlled trial. Psychol Med. 2008;38(2):279-287.

127. Coventry PA, Hudson JL, Kontopantelis E, et al. Characteristics of effective collaborative care for treatment of depression: A systematic review and meta-regression of 74 randomised controlled trials. PLoS One. 2014;9(9):e108114.

128. Baumeister H, Hutter N. Collaborative care for depression in medically ill patients. Curr Opin Psychiatry. 2012;25(5):405-414.

129. Horn EK, van Benthem TB, Hakkaart-van Roijen L, et al. Cost-effectiveness of collaborative care for chronically ill patients with comorbid depressive disorder in the general hospital setting, a randomised controlled trial. BMC Health Serv Res. 2007;7:28.

130. Li M, Kennedy EB, Byrne N, et al. Management of depression in patients with cancer: A clinical practice guideline. 2015.

131. Tully PJ, Baumeister H. Collaborative care for comorbid depression and coronary heart disease: A systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2015;5(12):e009128-2015-009128.
132. Atlantis E, Fahey P, Foster J. Collaborative care for comorbid depression and diabetes: A systematic review and meta-analysis. BMJ Open. 2014;4(4):e004706-2013-004706.

133. Huang Y, Wei X, Wu T, Chen R, Guo A. Collaborative care for patients with depression and diabetes mellitus: A systematic review and meta-analysis. BMC Psychiatry. 2013;13:260-244X-13-260.

134. van der Feltz-Cornelis CM, Nuyen J, Stoop C, et al. Effect of interventions for major depressive disorder and significant depressive symptoms in patients with diabetes mellitus: A systematic review and meta-analysis. Gen Hosp Psychiatry. 2010;32(4):380-395.

135. Panagioti M, Bower P, Kontopantelis E, et al. Association between chronic physical conditions and the effectiveness of collaborative care for depression: An individual participant data meta-analysis. JAMA Psychiatry. 2016;73(9):978-989.

136. van Eck van der Sluijs,J, Castelijns H, Eijsbroek V, van der Feltz-Cornelis CM. Effectiveness of collaborative care for patients with a combination of physical and psychiatric problems: A review and meta-analyses. J Psychosom Res. 2016;73(9):85-85.

137. Grochtdreis T, Brettschneider C, Wegener A, et al. Cost-effectiveness of collaborative care for the treatment of depressive disorders in primary care: A systematic review. PLoS One. 2015;10(5):e0123078.

138. Goorden M, Huijbregts KM, van Marwijk HW, Beekman AT, van der Feltz-Cornelis CM, Hakkaart-van Roijen L. Cost-utility of collaborative care for major depressive disorder in primary care in the netherlands. J Psychosom Res. 2015;79(4):316-323.

139. Goorden M, Vlasveld MC, Anema JR, et al. Cost-utility analysis of a collaborative care intervention for major depressive disorder in an occupational healthcare setting. J Occup Rehabil. 2014;24(3):555-562.

140. Simon GE, Katon WJ, Lin EH, et al. Cost-effectiveness of systematic depression treatment among people with diabetes mellitus. Arch Gen Psychiatry. 2007;64(1):65-72.

141. Frankel SA, Bourgeois JA, Erdberg P, eds. Comprehensive care for complex patients: The medical psychiatric coordinating physican model. 1st ed. New York: Cambridge University Press; 2013.

142. van der Feltz-Cornelis CM, Ader HJ. Randomization in psychiatric intervention research in the general practive setting. Int J Integr Care. 2009;9(e83).

143. Krol M, Papenburg J, Tan SS, Brouwer W, Hakkaart L. A noticeable difference? productivity costs related to paid and unpaid work in economic evaluations on expensive drugs. Eur J Health Econ. 2016;17(4):391-402.

144. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: The role of cost-effectiveness acceptability curves. Health Econ. 2001;10(8):779-787.

145. RVZ. Zinnige en duurzame zorg: Advies uitgebracht door de raad voor de volksgezondheid en zorg aan de minister van volksgezondheid, welzijn en sport. 2006.

146. Chavannes NH, Sont JK, van der Boog PJ, Assendelft WJ. E-health in chronic diseases: Not yet feasible for everyone in every setting. Ned Tijdschr Geneekd. 2012;156(A5345).

147. Car J, Huckvale K, Hermens H. Telehealth for long term conditions. BMJ. 2012;344:e4201.

148. Takahashi PY, Pecina JL, Upatising B, et al. A randomized controlled trial of telemonitoring in older adults with multiple health issues to prevent hospitalizations and emergency department visits. Arch Intern Med. 2012;172(10):773-779.

149. van der Feltz-Cornelis CM. Comorbid diabetes and depression: Do E-health treatments achieve better diabetes control? Diabetes Manag. 2013;3(5):379-388.

150. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Lowe B. Anxiety disorders in primary care: Prevalence, impairment, comorbidity, and detection. Ann Intern Med. 2007;146(5):317-325.

151. Roy-Byrne PP, Wagner A. Primary care perspectives on generalized anxiety disorder. J Clin Psychiatry. 2004;65 Suppl 13:20-26.

152. Roy-Byrne PP, Wagner AW, Schraufnagel TJ. Understanding and treating panic disorder in the primary care setting. J Clin Psychiatry. 2005;66 Suppl 4:16-22.

153. Lieb R, Becker E, Altamura C. The epidemiology of generalized anxiety disorder in europe. Eur Neuropsychopharmacol. 2005;15:445-452.

154. Olatunji BO, Cisler JM, Tolin DF. Quality of life in the anxiety disorders: A meta-analytic review. Clin Psychol Rev. 2007;27(5):572-581.

155. Beard C, Weisberg RB, Keller MB. Health-related quality of life across the anxiety disorders: Findings from a sample of primary care patients. J Anxiety Disord. 2010;24(6):559-564.

156. Bereza BG, Machado M, Einarson TR. Systematic review and quality assessment of economic evaluations and quality-of-life studies related to generalized anxiety disorder. Clin Ther. 2009;31(6):1279-1308.

157. Barrera TL, Norton PJ. Quality of life impairment in generalized anxiety disorder, social phobia, and panic disorder. J Anxiety Disord. 2009;23(8):1086-1090.

158. Andlin-Sobocki P, Wittchen HU. Cost of anxiety disorders in europe. J Clin Psychiatry. 2002;12(1):39-44.

159. Stein MB, Sherbourne CD, Craske MG, et al. Quality of care for primary care patients with anxiety disorders. Am J Psychiatry. 2004;161(12):2230-2237.

160. Stein MB, Roy-Byrne PP, Craske MG, et al. Quality of and patient satisfaction with primary health care for anxiety disorders. J Clin Psychiatry. 2011;72(7):970-976.

161. Fernandez A, Haro JM, Martinez-Alonso M, et al. Treatment adequacy for anxiety and depressive disorders in six european countries. Br J Psychiatry. 2007;190:172-173.

162. Smolders M, Laurant M, Roberge P, et al. Knowledge transfer and improvement of primary and ambulatory care for patients with anxiety. Can J Psychiatry. 2008;53(5):277-293.

163. Heuzenroeder L, Donnelly M, Haby MM, et al. Cost-effectiveness of psychological and pharmacological interventions for generalized anxiety disorder and panic disorder. Aust N Z J Psychiatry. 2004;38(8):602-612.

164. Prins MA, Verhaak PF, van der Meer K, Penninx BW, Bensing JM. Primary care patients with anxiety and depression: Need for care from the patient's perspective. J Affect Disord. 2009;119(1-3):163-171.

165. Walters K, Buszewicz M, Weich S, King M. Help-seeking preferences for psychological distress in primary care: Effect of current mental state. Br J Gen Pract. 2008;58(555):694-698.
166. van Schaik DJ, Klijn AF, van Hout HP, et al. Patients' preferences in the treatment of depressive disorder in primary care. Gen Hosp Psychiatry. 2004;26(3):184-189.

167. Nadiga DN, Hensley PL, Uhlenhuth EH. Review of the long-term effectiveness of cognitive behavioral therapy compared to medications in panic disorder. Depress Anxiety. 2003;17(2):58-64.

168. Bakker IM, van Marwijk HW, Terluin B, Anema JR, van Mechelen W, Stalman WA. Training GP's to use a minimal intervention for stress-related mental disorders with sick leave (MISS): Effects on performance: Results of the MISS project; a cluster-randomised controlled trial [ISRCTN43779641. Patient Educ Couns. 2010;78(2):206-211.

169. Katon W, Von Korff M, Lin E, Simon G. Rethinking practitioner roles in chronic illness: The specialist, primary care physician, and the practice nurse. Gen Hosp Psychiatry. 2001;23(3):138-144.

170. Roy-Byrne PP, Katon W, Cowley DS, Russo J. A randomized effectiveness trial of collaborative care for patients with panic disorder in primary care. Arch Gen Psychiatry. 2001;58(9):869-876.

171. Roy-Byrne PP, Craske MG, Stein MB, et al. A randomized effectiveness trial of cognitive-behavioral therapy and medication for primary care panic disorder. Arch Gen Psychiatry. 2005;62(3):290-298.

172. Roy-Byrne P, Craske MG, Sullivan G, et al. Delivery of evidence-based treatment for multiple anxiety disorders in primary care: A randomized controlled trial. JAMA. 2010;303(19):1921-1928.

173. van Steenbergen-Weijenburg KM, van der Feltz-Cornelis CM, Horn EK, et al. Cost-effectiveness of collaborative care for the treatment of major depressive disorder in primary care. A systematic review. BMC Health Serv Res. 2010;10:19.

174. Joesch JM, Sherbourne CD, Sullivan G, Stein MB, Craske MG, Roy-Byrne P. Incremental benefits and cost of coordinated anxiety learning and management for anxiety treatment in primary care. Psychol Med. 2011:1-12.

175. Katon W, Russo J, Sherbourne C, et al. Incremental cost-effectiveness of a collaborative care intervention for panic disorder. Psychol Med. 2006;36(3):353-363.

176. Katon WJ, Roy-Byrne P, Russo J, Cowley D. Cost-effectiveness and cost offset of a collaborative care intervention for primary care patients with panic disorder. Arch Gen Psychiatry. 2002;59(12):1098-1104.

177. Muntingh AD, van der Feltz-Cornelis CM, van Marwijk HW, et al. Collaborative stepped care for anxiety disorders in primary care: Aims and design of a randomized controlled trial. BMC Health Serv Res. 2009;9:159.

178. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: Psychometric properties. J Consult Clin Psychol. 1988;56(6):893-897.

179. Terluin B, Van Heest FB, Van der Meer K, et al. NHG-standaard angststoornissen. Huisarts en Wetenschap. 2004;47(1):26-37.

180. Oostenbrink JB, Bouwmans CAM, Koopmanschap MA. Handleiding voor kostenonderzoek, methoden en standaardkostprijzen voor economische evaluaties in de gezondheidszorg (manual for research on costs, methods and standardized cost prices for economic evaluation in health care). 2004.

181. Koopmans GT, Lamers LM. Is the impact of depressive complaints on the use of general health care services dependent on severity of somatic morbidity? J Psychosom Res. 2006;61(1):41-50.

182. Katon WJ, Roy-Byrne P, Russo J, Cowley D. Cost-effectiveness and cost offset of a collaborative care intervention for primary care patients with panic disorder. Arch Gen Psychiatry. 2002;59(12):1098-1104.

183. Scogin FR, Hanson A, Welsh D. Self-administered treatment in stepped-care models of depression treatment. J Clin Psychol. 2003;59(3):341-349.

184. Broman CL, Reckase MD, Freedman-Doan CR. The role of parenting in drug use among black, latino and white adolescents. J Ethn Subst Abuse. 2006;5(1):39-50.

185. Choquet M, Hassler C, Morin D, Falissard B, Chau N. Perceived parenting styles and tobacco, alcohol and cannabis use among french adolescents: Gender and family structure differentials. Alcohol Alcohol. 2008;43(1):73-80.

186. Hoeve M, Dubas JS, Gerris JR, van der Laan PH, Smeenk W. Maternal and paternal parenting styles: Unique and combined links to adolescent and early adult delinquency. J Adolesc. 2011;34(5):813-827.

187. Kristjansson AL, Sigfusdottir ID, Allegrante JP. Adolescent substance use and peer use: A multilevel analysis of cross-sectional population data. Subst Abuse Treat Prev Policy. 2013;8:27-597X-8-27.

188. Curcio AL, Mak AS, George AM. Do adolescent delinquency and problem drinking share psychosocial risk factors? A literature review. Addict Behav. 2013;38(4):2003-2013.

189. Liddle HA, Rowe CL, Dakof GA, Ungaro RA, Henderson CE. Early intervention for adolescent substance abuse: Pretreatment to posttreatment outcomes of a randomized clinical trial comparing multidimensional family therapy and peer group treatment. J Psychoactive Drugs. 2004;36(1):49-63.

190. Carr A. The effectiveness of family therapy and systemic interventions for child-focused problems. Journal of Family Therapy. 2008;31(1):3-4.

191. Retzlaff R, von Sydow K, Beher S, Haun MW, Schweitzer J. The efficacy of systemic therapy for internalizing and other disorders of childhood and adolescence: A systematic review of 38 randomized trials. Fam Process. 2013;52(4):619-652.

192. Hendriks V, van der Schee E, Blanken P. Treatment of adolescents with a cannabis use disorder: Main findings of a randomized controlled trial comparing multidimensional family therapy and cognitive behavioral therapy in the netherlands. Drug Alcohol Depend. 2011;119(1-2):64-71.

193. Van der Stouwe T, Asscher JJ, Stams GJ, Deković M, van der Laan PH. The effectiveness of multisystemic therapy (MST): A meta-analysis. Clinical psychology review. 2014;34(6):468-481.

194. Morgan TB, Crane DR. Cost-effectiveness of family-based substance abuse treatment. J Marital Fam Ther. 2010;36(4):486-498.

195. Shemilt I, Mugford M, Byford S, et al. Incorporating economics evidence. In: Higgins J.P.T. GS, ed. Cochrane handbook for systematic reviews of interventions. 5.1.0. ed. handbook.cochrane.org.: The Cochrane Collaboration; 2011.

196. Drummond M.F. JTO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. the BMJ economic evaluation working party. BMJ. 1996;313(7052):275-283.
197. French MT, Roebuck MC, Dennis ML, Godley SH, Liddle HA, Tims FM. Outpatient marijuana treatment for adolescents. economic evaluation of a multisite field experiment. Eval Rev. 2003;27(4):421-459.

198. Sheidow AJ, Bradford WD, Henggeler SW, et al. Treament costs for youths receiving multisystemic therapy or hospitalization after a psychiatric crisis. Psych Serv. 2004;55(5):548-554.

199. McCollister KE, French MT, Sheidow AJ, Henggeler SW, Halliday-Boykins CA. Estimating the differential costs of criminal activity for juvenile drug court participants: Challenges and recommendations. J Behav Health Serv Res. 2009;36(1):111-126.

200. French MT, Zavala SK, McCollister KE, Waldron HB, Turner CW, Ozechowski TJ. Cost-effectiveness analysis of four interventions for adolescents with a substance use disorder. J Subst Abuse Treat. 2008;34(3):272-281.

201. Olsson TM. MST with conduct disordered youth in sweden: Costs and benefits after 2 years. Res Social Work Prac. 2010;20(2):561-571.

202. Sheidow AJ, Jayawardhana J, Bradford WD, Henggeler SW, Shapiro SB. Money matters: Cost effectiveness of juvenile drug court with and without evidence-based treatments. J Child Adolesc Subst Abuse. 2012;21(1):69-90.

203. Cary M, Butler S, Baruch G, Hickey N, Byford S. Economic evaluation of multisystemic therapy for young people at risk for continuing criminal activity in the UK. PLoS One. 2013;8(4):e61070.

204. Dennis M, Godley SH, Diamond G, et al. The cannabis youth treatment (CYT) study: Main findings from two randomized trials. J Subst Abuse. 2004;27:197-213.

205. Dopp AR, Borduin CM, Wagner DV, Sawyer AM. The economic impact of multisystemic therapy through midlife: A cost-benefit analysis with serious juvenile offenders and their siblings. J Consult Clin Psychol. 2014;82(4):694-705.

206. Borduin CM, Dopp AR. Economic impact of multisystemic therapy with juvenile sexual offenders. J Fam Psychol. 2015;29(5):687-696.

207. Schoenwald SK, Ward DM, Henggeler SW, Pickrel SG, Patel H. Multisystemic therapy treatment of substance abusing or dependent adolescent offenders: Costs of reducing incarceration, inpatient and residential treatment. J Child Fam Stud. 1996;5(4):431-444.

208. McCollister KE, French MT, Sheidow AJ, Henggeler SW, Halliday-Boykins CA. Estimating the differential costs of criminal activity for juvenile drug court participants: Challenges and recommendations. J Behav Health Serv Res. 2009;36(1):111-126.

209. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL, eds. Methods for the economic evaluation of health care programs. 3rd ed. Oxford: Oxford University press; 2005.

210. Liddle HA. A multidimensional model for treating the adolescent who is abusing alcohol and other drugs. In: Snyder W, Ooms T, eds. Empowering families, helping adolescents: Family-centered treatment of adolescents with alcohol, drug abuse and other mental health problems. 1st ed. Washington, DC: United States Public Health Service; 1991.

211. Leukefeld C, Gullotta TP, Staton-Tindall M. Adolescent substance abuse: Evidence-based approaches to prevention and treatment. 1st ed. New York: Springer; 2008.

212. Oudhof M, ter Berge I, Berger M. Checklist MST/FFT: De ontwikkeling van een indicatie-instrument voor MST en FFT in de vorm van een checklist. 2009.

213. Tanner-Smith EE, Wilson SJ, Lipsey MW. The comparative effectiveness of outpatient treatment for adolescent substance abuse: A meta-analysis. J Subst Abuse Treat. 2013;44(2):145-158.

214. Copeland J, Swift W. Cannabis use disorder: Epidemiology and management. International Review of Psychiatry. 2009;21:96-103.

215. Sharma L, Markon KE, Clark LA. Toward a theory of distinct types of "impulsive" behaviors: A meta-analysis of self-report and behavioral measures. Psychol Bull. 2014;140(2):374-408.

216. Volkow ND, Fowler JS, Wang GJ. The addicted human brain: Insights from imaging studies. J Clin Invest. 2003;111(10):1444-1451.

217. Goldstein PJ. The drugs/violence nexus: A tripartite conceptual framework. Journal of Drug Issues. 1985;39:143-174.

218. Fergusson DM, Swain-Campbell NR, Horwood LJ. Deviant peer affiliations, crime and substance use: A fixed effects regression analysis. J Abnorm Child Psychol. 2002;30(4):419-430.

219. Hendriks V, van der Schee E, Blanken P. Matching adolescents with a cannabis use disorder to multidimensional family therapy or cognitive behavioral therapy: Treatment effect moderators in a randomized controlled trial. Drug Alcohol Depend. 2012;125(1-2):119-126.

220. Webb C, Scudder M, Kaminer Y, Kadden R. The Motivational Enhancement Therapy and Cognitive Behavioral Therapy Supplement: 7 sessions of Cognitive Behavioral Therapy for Adolescent Cannabis Users, Cannabis youth treatment (CYT) Series. 2016;2.

221. Sampl S, Kadden R. Motivational Enhancement Therapy and Cognitive Behavioral Therapy for Adolescent cannabis users: 5 Sessions, Cannabis Youth Treatment (CYT) Series. 2001;1.

222. Elliott DS, Huizinga D, Ageton SS. Explaining deliquency and drug use. Beverly Hills, CA: Sage Publications; 1985.

223. BIVV. Kerncijfers verkeersveiligheid 2010. Brussel: Observatorium voor verkeersveiligheid; 2011.

224. Research and Documentation Centre (WODC), National Statistics Bureau (CBS), Council for the Judiciary. Criminaliteit en rechtshandhaving. Den Haag: Boorn uitgevers; 2012.

225. Achenbach TM, Rescorla LA. Manual for the ASEBA School-age Forms and Profiles. University of Vermont, Research center for Children, Youth, and Families.

226. van Reenen M, Janssen B, Oppe M, Kreimeier S, Greiner W. EQ-5D-Y user guide: Basic information on how to use the EQ-5D-Y instrument. 2014.

227. Byford S. The validity and responsiveness of the EQ-5D measure of health-related quality of life in an adolescent population with persistent major depression. J Ment Health. 2013;22(2):101-110.

228. Fredheim T, Danbolt LJ, Haavet OR, Kjønsberg K, Lien L. Collaboration between general practitioners and mental health care professionals: A qualitative study. International Journal of Mental Health Systems. 2011;5(13):2-7.

229. Ramsey S, Willke R, Briggs A, et al. Good research practices for cost-effectiveness analysis alongside clinical trials: The ISPOR RCT-CEA task force report. Value in Health. 2005;8(5):521-533.

230. Brouwer WBF, Koopmanschap MA, Rutten FH. Productivity costs through quality of life? A response to the recommendation of the washington panel. Health economics. 1997;6:253-259.

231. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness AnalysesSecond panel on cost-effectiveness in health and medicine JAMA. 2016;316(10):1093-1103.

232. Research and Documentation Centre (WODC). Vragenlijst internationaal onderzoek selfreport delictgedrag [questionnaire international study self-report delinquency]. Den Hague: Wetenschappelijk Onderzoek en Documentatie Centrum (WODC); 1991.

233. Knollmann M, Knoll S, Reissner V, Metzelaars J, Hebebrand J. School avoidance from the point of view of child and adolescent psychiatry: Symptomatology, development, course, and treatment. Dtsch Arztebl Int. 2010;107(4):43-49.

234. van Reenen M. EQ-5D-5L user guide. EuroQol Research Foundation. 2015.

235. Feng Y, Devlin N, Herdman M. Assessing the health of the general population in england: How do the three- and five-level versions of EQ-5D compare? Health and Quality of Life Outcome. 2015;13:171.

236. Agborsangaya CB, Lahtinen M, Cooke T, Johnson JA. Comparing the EQ-5D 3L and 5L: Measurement properties and association with chronic conditions and multimorbidity in the general population. Health and Quality of Life Outcomes. 2014;12:74.

237. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: A multi-country study . Quality of Life Research. 2013;22(7):1717-1727.

238. Ferreira LN, Ferreira PL, Ribeiro FP, Pereira LN. Comparing the performance of the EQ-5D-3L and the EQ-5D-5L in young portuguese adults. Health and Quality of Life Outcomes. 2016;14:89.

239. Berghmans R, Berg M, van den Burg M, ter Meulen R. Ethical issues of cost effectiveness analysis and guideline setting in mental health care. J Med Ethics. 2004;30(2):146-150.

240. Magnee T, de Beurs DP, Kok TY, Verhaak PF. Exploring the feasibility of new dutch mental health policy within a large primary health care centre: A case study. Fam Pract. 2017.