The case
for stepped care

Exploring the applicability and cost-utility

of stepped-care strategies

in the management

of depression

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VRIJE UNIVERSITEIT

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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor of Philosophy
aan de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. V. Subramaniam,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op woensdag 7 november 2018 om 15.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

Jolanda Antonia Cornelia Meeuwissen

geboren te Borsele

promotoren: prof.dr. A.J.L.M. van Balkom
prof.dr. H.F.E. Smit

Promotores

Prof.dr. A.J.L.M. (Ton) van Balkom, Professor of Evidence-Based Psychiatry, Department of Psychiatry, Amsterdam UMC, VU University, Amsterdam.

Prof.dr. H.F.E. (Filip) Smit, Professor of Evidence-Based Public Mental Health, Department of Epidemiology and Biostatistics, VU University Medical Centre, Amsterdam.

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Prof.dr. B. (Bea) Tiemens, Appointed Professor of Evidence based practice in mental health care, Radboud University Nijmegen, Faculty of Social Science

Voor mijn lieve ouders Gertjan & Corrie
En voor lieve Roy & lieve Rutger
Door jullie is alles mogelijk!

"One can have no smaller or greater mastery than mastery of oneself."
Leonardo Da Vinci, 1452-1519

Contents

Chapter 1
General introduction

1.1 Stepped care: a micro-, meso-, and macroperspective

In this thesis, it will be clarified that stepped care is concurrently about:

1 Supporting decision making (a microperspective)

2 Integrating care (a mesoperspective)

3 Improving the cost-utility of care (a macroperspective).

A microperspective

The therapeutic process can be seen as the primary process in mental health care, in which the patient is placed central. This patient-centred view is regarded as the microperspective on depression care in this thesis. From this patient-centred view, contributing to the therapeutic process implies: all that the care professional, together with the patient, performs to establish, accomplish, evaluate or adjust an individual treatment strategy (including diagnostics and treatment interventions) for the direct benefit of the patient. In this therapeutic process many clinical decisions, often complex, need to be made. Always under uncertainty, sometimes under time pressure too.

Stepped care contains three elements that are essential in support of the therapeutic process (Meeuwissen & Donker 2004):

1 Choosing the least intensive intervention possible, taking into account the nature, duration, severity and course of symptoms, from the treatment alternatives to reach individual treatment goals;

2 Routinely monitoring the progress of symptoms and evaluating treatment outcomes;

3   Based on observed treatment outcomes, adjusting the individual treatment by stepping up to a more intensive treatment intervention, until treatment goals are reached.

As thus, with a stepped-care strategy, care is intensified gradually according to patient's *needs*. When treatment goals are achieved or patient's needs are changed, for example when remission is reached, this strategy is repeated for new treatment goals, such as relapse prevention or full recovery.

A mesoperspective

The setting in which care professionals operate, shapes conditions for the therapeutic process. A mesoperspective on care emphasizes that organisational frameworks can intermediate macrolevel influences and create effects on the microlevel (Dopfer, Foster & Potts 2004). In this thesis, we assume that an amount of uncertainty in the therapeutic process can be reduced by means of stepped care. This reduction in uncertainty can be reached not only by supporting clinical decision making, but also by integrating care processes at the mesolevel, in the healthcare institutions, units, programmes, care practices, care groups or other care settings. Care processes can be integrated in such a way that the conditions for an optimal therapeutic process are improved by means of, for example, the implementation of evidence-based clinical practice guidelines, methods for routine outcome monitoring and protocols for multidisciplinary care coordination.

With stepped care a more cost-effective allocation of scarce resources is expected (Davison 2000; Haaga 2000). It is assumed that stepped care will allow current healthcare resources to be used more efficiently (efficiency assumption), since low-intensity interventions can provide significant health gain for at least a proportion of patients (equivalence assumption) (Bower & Gilbody 2005).

A mesoperspective

An efficient allocation is not a guarantee for an equitable allocation of health resources (Culyer 2015). In improving the cost-effectiveness of depression care, a broad macroperspective that also considers population's health and equity in distributing health is paramount. Improvements on the mesolevel in part of the care continuum or for some groups of patients, should not entail adverse effects on other parts or for other patients in depression care. The assumption is that stepped care can result in more health gains than care as usual in terms of cost-utility, and in terms of health gains for more patients. By means of a better allocation of resources through stepped care, more patients are expected to benefit.

This chapter introduces the key concepts in this thesis and explains relevant developments, indicates their applicability in depression care and why depressive disorder is such an obvious case example for stepped care. The research questions and objectives of this thesis are formulated, and outlined is how we address these research questions.

1.2 Key concepts and relevant developments

1.2.1 Decision making in health care

This thesis relates to the question *'What treatment, given by whom, and under what circumstances, is the most effective for this patient with this specific problems?'* (Paul 1967). Even at the times of evidence-based mental health care, or maybe more often than ever before, this classical question cannot be answered with certainty. This uncertainty is what care professionals and their patients need to deal with in performing the therapeutic process. This also holds concerning patients with a depression.

Decision making in mental health care is complex by nature, and this accounts both in clinical practice and on a healthcare policy level (Eddy 1984; Bornstein & Emler 2001; Marewski & Gigerenzer 2012). While the number of treatment options that improve the prognosis and outcomes of many conditions increased over the last decennia, as well as the range of possible diagnoses, making healthcare decisions even more complex, the growing evidence-base to inform decision making is never complete and not conclusive (Bhugra et al. 2011; Norcross & Wampold 2011).

Uncertainties in clinical decision making may concern the diagnosis, the natural history of the disease, the current state of the patient, the prognosis, the treatment effects, and the risks of treatment (Bhugra et al. 2011; Norcross & Wampold 2011). In healthpolicy making, uncertainty also concerns the effects of an intervention in a group or population as a whole (Hunink, Glasziou, Siegel, Weeks, Pliskin, Elstein & Weinstein 2001). The *values* of care involve uncertainty as well, since these are often not specified by the stakeholders involved. There may be multiple competing objectives regarding the outcomes desired to achieve or to avoid (Zimmerman et al. 2006; Gray 2007; 2013; Porter 2008; 2010; Gray & Porter 2009; Porter & Teisberg 2004).

Best available evidence, as well as clinical intuition and experience on expected benefits and risks, need to be counterbalanced with individual patient preferences, values embodied by patients and society, and costs of care, considered on both the short-term and long-term (Hunink et al. 2001). An *optimal* treatment strategy to achieve a treatment goal can thus be defined as a sequence of choices at critial decision points that leads to the *maximum* value considered the probability of all desired and undesired outcomes.

We know from cognitive psychology that decision making under uncertainty is biased by reliance on unconscious heuristics in cognitive processing that can be very useful, but can also lead to errors in prediction or estimation (Tversky & Kahneman 1974). Examples of these heuristics are: representiveness, often employed when people judge the probability that a case or an event belongs

to a category or process; availability of instances or scenarios, often employed when asked to assess the frequency of a class or the plausibilty of a particular development; and adjustment to an anchor, when an initial value or starting point for the formulation of a problem is adjusted to yield the answer (Tversky & Kahneman 1974). Also experienced clinicians (and researchers) are prone to biases (Delgadillo, Gellatly & Stephenson-Bellwood 2015). Most decision making in health care contains an irreducible intuitive element that relies on these heuristics, although uncertainty can be reduced to a degree (Hall 2002). Where the outcome of decisions is important and the investments are large, it is encouraged to make careful and responsible decisions, that may be provisional and adjusted when needed according to new insights (Hertz 2013). This applies in mental health care. Patients, care professionals, and policymakers alike should be aware that our decisions are vulnerable to cognitive biases, otherwise this can affect the outcome in an unfavourable way.

1.2.2 Evidence-based guidance

To reduce uncertainty in decision making in health care, evidence-based guidelines are being developed (Eddy 1982; 1996; Gray 1997; Haynes & Haines 1998). The development of these clinical practice guidelines is pursued from the evidence-based mental health (EBMH) paradigm to support care professionals. Evidence-based practice intends to integrate the values and preferences of the patient as well as professional expertise, together with the best evidence to inform the decision making process on patient care, into decisions that enhance the likelihood of optimal health outcomes.

The best evidence is found in research that has been conducted using sound methodology, critically appraised for its validity and clinical relevance (Sackett et al. 2000; Straus, Glasziou, Richardson & Haynes 2010). Continuous improvements keep the evidence-based paradigm vivid. Within the evidence-based paradigm, the gold standard has changed from the randomised controlled trial (Cochrane 1972) to the systematic review and meta-analysis of randomised controlled trials (Cochrane Library 2014; Seshia & Young 2013). Also, the emphasis has shifted from the conscientious, explicit, and judicious use of best evidence (Sackett et al. 1996) to best value for patients (Sackett et al. 2000; Straus et al. 2010). *Individualised* guidelines can combine readily available patient characteristics with the expected benefit from treatment alternatives for the patient (Eddy 2011). *Personalising* the evidence on differing probabilities, risks, and benefits of the patient's options can take into account the individual patient's preferences (Gray 2013). According to Culyer (2015): 'Good decisions need to be *informed* by evidence and a good appreciation of how variable and contestable evidence can be; and they need also to be informed by values, and good appreciation that values are not always shared, may conflict, and vary in moral worth.'

To overcome biases in clinical reasoning and decision making, and thus to reduce uncertainty, also evidence-based decision tools are being developed to support care professionals, such as algorithms, flow charts, or other decision aids (Smith & Gilhooly 2006; Trivedi 2002; Trivedi et al. 2004; Trivedi, Lin & Katon 2007; Klinkman 2003; Sobell & Sobell 2000). These decision support tools can be seen as explicit heuristics with simple decision strategies that ignore part of the available information, basing decisions on only the few relevant predictors (Marewski & Gigerenzer 2012). In these decision support tools, the treatment alternatives are summarised for each decision point in the therapeutic process in a structured sequence that is guiding care professionals (and their patients) to recommended actions. Decision support tools enable to make our assumptions explicit and clarify our goals systematically. They supply the evidence and help to think through the consequences at each decision point and the likelihood of desired and undesired outcomes or following disease states or events. Besides improving decision making in uncertainty, they can help to communicate in a logical way (Hunink et al. 2001).

An optimal clinically useful decision guide should give information about how outcomes of a recommended practice are likely to vary with different patient characteristics and, in addition, outcomes should be presented in a way that includes patients preferences (Hunink et al. 2001). Optimisation and individually tailoring of decision tools include the collecting and evaluating, weighing and combining all needed information to maximise the chances of attaining goals. In optimising a decision tool, increased complexity may limit its use in clinical practice (Hunink et al. 2001). To assure that treatment goals are achieved while unwanted consequences are avoided, it is important that information that is most relevant for the decisions to be made, becomes explicitly avaiblable using a 'fast and frugal' decision tool (Marewski & Gigerenzer 2012).

As we explore in this thesis, decision tools for stepped-care strategies can support decision making and provide this much needed guidance in depression care.

1.2.3   Matched care, the alternative approach

The added value of stepped care to the therapeutic process can be explained by a comparison to matched care. Stepped care and matched care both approach decisions to be made on the match between patient and treatment from the assumption that for different patients, different types of treatment are appropriate. Both approaches acknowledge that response to treatment varies widely among patients, even with the same disorder, and not all patients with the same disorder benefit from the same type, duration or frequency of treatment (Paul 1967; Norcross & Wampold 2011). From a matched-care approach it is assumed that characteristics of individual patients that can have differential effects on specific treatments can be identified *prior* to starting treatment, in order to determine the

best match between a patient with certain characteristics and a specific treatment (Mattson & Allan 1991; Mattson 1994). These patient characteristics can be sociodemographic factors, clinical characteristics such as symptom patterns or comorbidities, or biological markers such as genetic variation (Simon & Perlis 2010). Matching to patient preferences, like for a male or female care professional, or regarding the use of antidepressant medication, is not what is mentioned with matched care in this thesis. Preference-led matching can be part of the decision making process in matched care as well as in stepped care to improve the therapeutic relationship or treatment outcomes (van Schaik et al. 2004; Lin et al. 2005; Gelhorn et al. 2011; van Beljouw et al. 2014).

The matched-care approach originates from the aptitude (or attribute)-treatment interaction (ATI) research paradigm, that analyses interactions between patient and treatment variables instead of searching for only main effects that give insight into the average effectiveness of treatments (Edwards & Cronbach 1952; Cronbach 1957; Snow 1991; Caspi & Bell 2004). Matching factors need to be distinghuised from outcome predictors, that affect outcomes from all different treatments in the same way but have no differential effect on specific treatments (Mattson 1994; Simon & Perlis 2010). Understanding outcome predictors can be helpful in reducing uncertainty around the individual prognosis and response to treatment. What a matched-care approach adds is the search for the true moderators of treatment effect, i.e. the patient characteristics that moderate the response to specific treatments. Only *true moderators* can be the matching factors. To develop practical algorithms for assigning patients to treatments is earlier expressed as an ultimate goal of treatment-matching research (Mattson 1994; Del Boca & Mattson 1994). A dynamic treatment-matching strategy is suggested in order to match patients with appropiate treatment regarding their different stages of recovery (Mattson 1994; Simon & Perlis 2010).

Accounting for clinical diversity is essential in stepped care as well as in matched care to maximise treatment outcomes. However, the treatment strategies that result from these different approaches can be very different. In matched-care strategies, patient characteristics will be extensively assessed prior to starting with treatment in order to find the most appropiate patient-treatment match (Simon & Perlis 2010; Mattson 1994). Instead, in stepped-care strategies, after initial treatment choice, more emphasis is placed on carefully monitoring progress during treatment and adjusting treatment accordingly as needed. This implies an important *trade-off* that needs to be made concerning treatment delay and erring on the safe side. Unless evidence is available about a specific patient-treatment match, stepped-care strategies start with the least intensive treatment that is appropiate for the patient, avoiding over-treatment. This is followed by stepping up to more intense treatment as needed based on observed outcomes of earlier interventions, avoiding undertreatment. Diagnostics take place to enable initial treatment choices, for example based on the nature and severity of symptoms and the patient's individual prognosis, while information from symptom monitoring or additional diagnostics

during the course of depression steers the further treatment strategy. This is a difference in principle from the matched-care approach that maybe in clinical practice sometimes would result in no difference at all.

Matching research has in the past decennia resulted in some indications that specific clinical characteristics may inform the choice between antidepressant medication and psychotherapy, and the choice of specific antidepressant medication or specific psychotherapy (Simon & Perlis 2010; Bockting et al. 2006). Although some matches between biomarkers and antidepressant medication are found to personalise medicine (f.e. Cattaneo et al. 2016), unfortunately the evidence for patient-treatment matches is still very limited (Simon & Perlis 2010; Cuijpers et al. 2012; McMahon & Insel 2012; McMahon 2015; Tiemens 2017). Above that, for clinical utility, not only should the matching factors be known prior to treatment, but also these need to be able to be identified or tested before the start of treatment in clinical practice (Weda, Jansen & Vonk 2017; Simon & Perlis 2010).

The patient-treatment matches or personalising factors found in research can be integrated in decision tools for stepped-care strategies. With more evidence becoming available, either both approaches may grow more and more towards each other, or matched-care strategies will make stepped-care strategies unnecessary. In the meantime, stepped-care strategies are supposed to support decision making under uncertainty in a valid, and a presumably risk-averting way.

1.2.4 Quality and efficiency improvement in health care

From the chronic care paradigm a transformation was made towards a more comprehensive and integrative health system for chronic care, proactively maintaining health and preventing or delaying disease, instead of a health system only reactively responding to acute episodes of illness (Von Korff et al. 1997; Von Korff & Tiemens 2000; Wagner et al. 2001). A proactive approach to health promotion aims to prevent the aggravation of problems at all stages in the course of, in this case, depression throughout the continuum of care, and to strengthen patients' capabilities to self-management of their disease state through psychoeducation, self-help skills and empowerment (Epstein & Sherwood 1996; Ellrodt et al. 1997; Weingarten et al. 2002).

The care improvement strategies mainly originate from the evidence-based framework of the Chronic Care Model adopted by the World Health Organization (Wagner 1998; WHO 2002; Coleman et al. 2009). Aimed is for improvement in both quality and efficiency by coordinating multidisciplinary care processes. At the same time, improvement of the effectiveness of individual treatments is aimed for, by using evidence-based guidelines and care standards for appropriate and high-quality care. This is intended to result in cost savings or cost control while improving quality and efficiency of care (Dellby 1996; Ellrodt et al. 1997; Wagner et

al. 2005). Diabetes mellitus (type 2) is one of the most common chronic conditions. In improving the management of chronic conditions, diabetes care is often seen as an example (Elissen 2013).

The shift to chronic care management approaches was determined by rising costs of care and prevailing quality deficiencies, such as fragmentation of services, insufficient evidence-based practice, inadequate follow up, lacking information systems and poor integration with community services (Wagner et al. 2001; IOM 2001). In anticipation of the ageing of populations, with increasing prevalences of chronic diseases and multimorbidity that will be accompanied by further rising healthcare costs and workforce shortages, more pressure has been put on the quality of health care (Wagner et al. 2001; IOM 2001). Besides the introduction of incentives for managed competition, the chronic care management approach and a programmatic approach to reach integrated health care, have been adapted to redesign health care in the Netherlands (Kruijff & Schreuder 1997; VWS 2008; Vrijhoef & Wagner 2010; Huijben 2011; Baan 2015; Kroneman, Boerma, van den Berg, Groenewegen, de Jong & van Ginneken 2016) resulting in the development of care standards for depression and other chronic diseases (for depression: Meeuwissen et al. 2007; Meeuwissen & van Bon, on behalf of the care standard development group 2018).

The economic crisis from 2008 that only since 2017 is called behind us, has put even more pressure on controlling healthcare costs and sustainable health care, while health systems, in general, need more, not fewer, resources in times of economic crisis (Thomson et al. 2014; ten Have et al. 2015). Just recovered from the economic crisis, policy-makers in Europe attempt to limit public spending through cuts to the health budget. For example, the Netherlands activated public revenue for the health insurance system by increasing contribution rates for health insurance and raising the ceiling on contributions, reduced benefit by coverage exclusions, and restricted acces to preventive services (Thomson et al. 2014; Boot 2015; Rutte et al. 2017).

Chronic care management has been critised for usually targeting at a group of patients with the same, single disorder only, while comorbidity and multimorbidity are highly prevalent. When the scarcity of healthcare resources is increasing, or even becoming more absolute, and decisions need to be made about the allocation of resources to maximise value for all the people in the population, the shift to population health management is made (Gray 2013). Stepped care can bring added value in depression care management (as further explained in chapter 3), when taking this macroperspective on health care.

1.3 Depression as a case example

The nature of depressive disorder, with substantial impact on quality of life for patients and their relatives, the high prevalence, substantial disease burden, and high accompanying costs, are making depressive disorder an obvious case example for stepped care in this thesis, especially considering the availability of clinical practice guidelines.

1.3.1 Symptoms, severity and comorbidity

Depression (Major Depressive Disorder, MDD, or major depression) is a mental disorder with emotional, cognitive and physical symptoms, that affects how one feels, thinks and behaves (American Psychiatric Association [APA] 2013). According to the DSM-criteria a person with depression has i) a depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful) and/or ii) a markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day, as indicated by either subjective account or observation made by others. One or both of these core symptoms are combined with: iii) significant weight loss or weight gain, or decrease or increase in appetite nearly every day; and/or iv) insomnia or hypersomnia nearly every day; and/or v) psychomotor agitation or retardation nearly every day observable by others; and/or vi) fatigue or loss of energy nearly every day; and/or vii) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick); and/or viii) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others; and/or ix) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. Five or more of these symptoms have been present during the same 2-week period and represent a change from previous functioning. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning and are not due to the direct physiological effects of a substance or a general medical condition, or mood-incongruent delusions or hallucinations.

Depression can be specified as mild, moderate or severe. Depression severity is based on the nature and number of symptoms, the severity of these symptoms and the degree in which functioning is limited (APA 2013). This severity can, with or without treatment, change during a depressive episode and during the course of depression (Judd et al. 1998). Also the duration of a depressive episode is variable. In the general population, reflecting the natural course of depression, the median duration of a depressive episode is three months which is lower than found in clinical populations (Spijker et al. 2002). The avarage duration of a depressive episode is

an estimated six months (Üstün et al. 2004). This estimation is based on epidemiological studies in subjects with depression in the community, including the Dutch NEMESIS study (Spijker et al. 2002).

Depression often occurs in comorbidity with somatic illness, such as diabetes (Egede & Ellis 2010; Verdurmen et al. 2006). Comorbid depression often goes unrecognised and is thereby perpetuated, and associated with further diminished health-related functioning and quality of life, as well as with exacerbation of the somatic illness. Major consequences of comorbid depression in diabetes are a non-active role or inactivity on the part of the patient, loss of energy, avoidance of social interaction, poor coping behaviour, poor treatment compliance and lack of disease control, and these contribute to worsening of both the physical and the mental illness (Pouwer et al. 2006; World Federation for Mental Health 2004).

1.3.2 Course and prognosis

The natural course of depression is highly variable (Bockting 2006; Spijker et al. 2002; Judd et al. 1998; Keller et al. 1992).

After a first episode of depression (of short or long duration), remission of symptoms can be either partial or complete. In a period of depression in partly or complete remission, the criteria for depression are not longer fulfilled within an interval of at least two months (APA 2013). A relapse of the depressive episode happens when symptoms return within two months before remission. Relapse rates of 21-50% within 12 months are found (Richards 2011).

When complete remission is continued during a two-month period, recovery from the depressive episode is reached. In the Netherlands, 50% of the general population with a depression recovered within 3 months, 63% within 6 months and 76% within 12 months (Spijker et al. 2002). After a period of complete remission, a new episode of depression, called a recurrence, may take place in about 60% after 5 years (67% after 10 years and 85% after 15 years) in specialised mental healthcare setting, and in 35% after 15 years in the general population (Hardeveld et al. 2010).

Once a recurrence occurred, the chance of more or multiple recurrent episodes increases with each new episode (Kessing et al. 2004; Solomon et al. 2000). When there is no recovery, and residual symptoms after an episode remain, the chance of recurrent episodes increases, and the time to recurrence decreases (Judd et al. 1998; 2000). This can lead to chronicity, in which symptoms persist for two years or longer, such as in persistent depressive disorder, although symptoms may be less severe or are fluctuating in severity (APA 2013). In the Dutch general population, nearly 20% of patients with a depression develops a chronic depression (Spijker 2002). Given a longer time frame with 6-year follow-up and including symptoms of affective and anxiety disorders, a portion of chronicity of 55% was found (Verduijn et al. 2017).

Depending on the varying course of depression, the need for care is often long-term, and depression should not be treated as a single episode requiring acute care, maybe repeatedly, only. The course of depression requires timely diagnostics and adequate intervention, that corresponds with the level of severity, the individual prognosis and early response to treatment (Kessing 2007; Judd et al. 1998; Wilson, Vitousek & Loeb, 2000; Ilardi & Craighead 1994). This also includes the prevention of relapses and recurrences (Bockting 2006) and treatment of chronic depression (Spijker et al. 2002; 2013).

Only few predictors of relapse or recurrence are known, and the number of previous episodes and subclinical residual symptoms appear to be the most important predictors (Richards 2011; Hardeveld et al. 2010; Paykel 2008; Bockting 2006; Spijker et al. 2002; Mueller et al. 1999). To support clinical decision making under this uncertainty throughout the course of depression, stepped-care strategies for depression management may be of added value in the aim to protect the patient from relapse or recurrence.

1.3.3 Prevalence, health loss and costs

The burden of depression has substantial impact on the quality of life, and the accompanying impairment of psychological functioning and social participation has a tremendous effect on individuals, their relatives and society (Ferrari et al. 2013). Due to the high prevalence at population level, combined with large disability weights, chronic diseases are by far the leading cause of disability in the world. Depression is the most prevalent mental chronic condition (RIVM 2013).

In the Netherlands, in the population aged 18-64 years, yearly 5.2% has a depression and 0.9% has dysthymia according to DSM-IV criteria (de Graaf et al. 2012). The lifetime-prevalence, representing the population that at some point in life experiences the condition, is 18.7% for depression and 1.3% for dysthymia (de Graaf et al. 2012). The prevalences are comparable to those in other Western-European countries (Kessler et al. 2007; Andrade et al. 2003). The ratio of one-year prevalence over lifetime prevalence, which can be seen as an indicator of the chronicity of depression, is relatively high (de Graaf et al. 2012).

The health loss due to a disease can be quantified as disability adjusted life years (DALYs). One DALY represents the loss of a healthy year of life and aggregates the years of life lived with disability (YLD) with the years of life lost due to premature mortality (YLL) (Mathers et al. 2002). Depressive disorders are the second leading cause of global disability (in terms of YLDs) and the eleventh leading cause of global burden (in terms of DALYs) (Ferrari et al. 2013). Thus, depressive disorders are a leading direct cause of the global disease burden even though no mortality was attributed as the underlying cause (Ferrari et al. 2013). Depression accounts for 8.2% of global YLDs and dysthymia for 1.4%. Depression accounts for 2.5% of global DALYs and dysthymia for 0.5%. The disease burden

increased by 37.5% between 1990 and 2010 due to population growth and ageing. The 16 million suicide DALYs and almost 4 million ischemic heart disease DALYs found attributable to depression, increase the overall burden of depressive disorders from 3.0% to 3.8% of global DALYs.

Smit et al. (2006) calculated that the disability weight for depression in the Netherlands equals 0.46, implying that one year spent in depression is valued as six-and-a-half months in good health while the remaining 46% of the year is regarded as health loss. This mean disability weight is averaged over mild, moderate and severe depression, accounting for the prevalence per severity level and the accompanying disability weights (i.e. 0.14 for mild depression, 0.35 for moderate depression and 0.76 for severe depression) (Smit 2006). This mean disability weight is comparable to the 0.48 in the WHO Global Burden of Disease study (Üstün et al. 2004).

Smit et al. (2006) also calculated that the annual direct and indirect excess costs of depression per capita are € 2,278. For each person suffering from a depression these costs are added to the annual base-rate costs of € 1,025 for having a disorder generated by minor illnesses and injuries not directly related to the depression. Thus every person with depression generates a cost of € 4,403 per year. Per one million prevalent cases the excess costs for depression are 132 million euro a year annually (Smit et al. 2006). Indexed to the rates and prevalence of major depression in the Dutch population in 2011, with 588.528 adults in the 18-65 years age group with major depression according to DSM-III-R criteria, generating yearly about 2,438 euro healthcare costs per person, the total costs of major depression in the 18–65 age group sum up to over € 1.4 billion euro a year in the Netherlands, attributable to healthcare uptake and productivity losses due to absence from work (additional calculations by Smit).

1.3.4 Evidence-based clinical practice guidelines

A wide variety of evidence-based interventions is available in the treatment of depression. Evidence-based clinical practice guidelines for depression recommend stepped-care strategies for sequencing treatment options and outcome monitoring (Spijker et al. 2013; Spijker et al. 2010; van Weel-Baumgarten et al. 2012; National Collaborating Centre for Mental Health 2009; New Zealand Guidelines Group 2008). The revised Dutch Multidisciplinary Guideline for Depression (Third revision, Spijker et al. 2013), more than previous Dutch guidelines, enables care professionals to follow a stepped-care approach, with algorithms for sequential treatment strategies guided by outcome monitoring, accounting for symptom severity, duration and recurrency. However, these guidelines have not yet been fully implemented into daily practice for all care professionals and their patients (Hermens et al. 2014; Sinnema et al. 2013). Moreover, it is not yet common practice to monitor symptoms and evaluate treatment effects after the initial

diagnostics and start of treatment as part of an integrated approach (Nuijen et al. 2015).

1.4 Objectives and research questions addressed in this thesis

1.4.1 Objectives

In this thesis, the objective is to investigate the added value of stepped care i) to the therapeutic process in patients with depression, and ii) to depression care management.

The aim of this thesis is to advance care for patients with depression from respectively a micro-, meso- and macroperspective in the benefit of patients and public health.

1.4.2 Research questions

Research questions addressed in this thesis are the following.

A microperspective

- What are the core elements of stepped-care strategies for depression? (chapter 2)
- How can depression care management advance individual stepped-care strategies? (chapter 3)

Mesoperspective

- What can be the added value of stepped care in depression care management? (chapter 3)
- Is it feasible to implement a stepped-care algorithm in depression care? (chapter 4)
- Is stepped care acceptable for care professionals and patients and can it lead to quality improvement on the mesolevel? (chapter 5)
- Can a self-help intervention for comorbid depression and anxiety disorder be implemented in diabetes care? (chapter 6)

Macroperspective

- What is the effectiveness of depression care management programmes? Can the heterogeneity in outcomes be explained by clinical diversity? (chapter 7)

- Are stepped-care strategies, according to the Dutch evidence-based guideline recommendations, beneficial in term of cost-utility? (chapter 8)

1.5 Outline of this thesis

This thesis consists of three parts.

Part I

In Part I the topics of stepped care and depression care management are described in more detail from the three perspectives, based on a narrative review of the literature. In chapter 2 the principles of stepped care are explained from the micro-, meso- and macroperspective. Furthermore, the translation of these principles to stepped-care strategies and a stepped-care model for depression care are presented here.

In chapter 3 chronic care management strategies are introduced, with a focus on the added value of stepped care in chronic care management programmes. A model for the process of implementing and evaluating depression care management and stepped-care strategies is described.

Part II

Part II of this thesis is about quality improvement of depression care by means of developing, implementing and evaluating stepped care and depression care management on the micro- and mesolevel. Three empirical studies illustrate how implementation and evaluation of stepped-care and depression care management strategies are conducted by using the depression care management process model described in chapter 3.

In chapter 4, the feasibility of a stepped-care programme for depression management is evaluated in an uncontrolled pre-post study in primary and secondary care settings in a pilot region in the Netherlands. We developed and implemented a stepped-care algorithm for diagnostics and treatment of depression based on the Dutch Multidisciplinary Guideline for Depression. Care professionals working with the algorithm were supported by a liaison-consultation function. Adherence to the protocol was assessed by interviewing 28 care professionals of 235 patients with mild, moderate or severe major depression. Consultation and referral patterns between primary and secondary care were analysed in this 2½ year study.

The study in chapter 5 evaluates quality improvement in depression care on the mesolevel. The stepped-care approach is applied in bringing together healthcare professionals to work together, and in developing practical tools to bridge the gap between evidence-based knowledge and what is being actually used in daily routine practice. Implementation goals concern improving the uptake of the Dutch Multidisciplinary Guideline for Depression in daily practice by multidisciplinary care teams. A simplified stepped-care depression model consists of a care pathway with a first-step treatment level for patients with non-severe depression (brief or mild depression) and a second-step level for patients with severe depression. This stepped-care model was implemented with the Institute for Healthcare Improvement's Breakthrough method, that has addressed several of the most pressing issues in chronic health care. Thirteen multidisciplinary teams participated in the project. In total 101 care professionals were involved, and 536 patients were diagnosed. Besides qualitative data, twelve months data were on recovery, as measured with the Beck Depression Inventory (BDI), and several process indicators were measured by the teams. Key variables in the strategy for change are described in relation to outcomes on the mesolevel.

Strategies for timely recognition and adequate treatment of mental disorders are needed for patients with type 2 diabetes mellitus. Self-help interventions for depression may constitute an appropriate first step in the treatment of depression comorbid with diabetes. Chapter 6 describes how depression management strategies that require minimal effort of the care professionals involved, were implemented in diabetes care. Aims of the 1½-year pilot study, an open clinical study with a pre-test post-test design, were to develop and evaluate a screening procedure followed by a guided self-help intervention for anxiety and depressive disorder in patients with type 2 diabetes mellitus in primary care. Seven specifically trained nurses screened 111 diabetes type 2 patients using a standardised screening interview. A psychiatric assessment of 53 patients who screened positive used a structured diagnostic interview. Sixteen patients fulfilling criteria for anxiety disorder or depression followed a self-help intervention guided by the nurse in 5 sessions. Follow-up assessment was at six months. A process evaluation took place half way the training and at the end of the pilot.

Part III

In part III of this thesis, the effectiveness of depression care management and the cost-effectiveness of stepped care are being evaluated, from a meso- and macroperspective. Chapter 7 presents a systematic review of reviews and empirical studies on chronic care management strategies for depression. We performed meta-analyses and meta-regression analyses to assess pooled effect estimates on care process and outcome measures. This review is part of a series analysing the effectiveness of chronic care management that besides depression includes COPD (Lemmens, Lemmens, Boom, Drewes, Meeuwissen, Steuten,

Vrijhoef, Baan 2011), heart failure (Drewes, Steuten, Lemmens, Baan, Boshuizen, Elissen, Lemmens, Meeuwissen & Vrijhoef 2012) and diabetes (Elissen, Steuten, Lemmens, Drewes, Lemmens, Meeuwissen, Baan & Vrijhoef 2012). We explore to what extent the observed heterogeneity can be explained by study quality, length of follow-up, number of components of the Chronic Care Model (CCM) and patient characteristics.

In chapter 8, the cost-utility of guideline-based stepped-care algorithms for depression is evaluated. We developed a depression state-transition model for economic evaluation by adapting the model by Vos (2005), distinghuising mild versus moderate and severe depression. Input parameters are based on research literature and expert knowledge of the Dutch Guideline Development Group. Analyses are conducted on treatment trajectories in several scenarios comparing care according to the Dutch Multidisciplinary Guideline for Depression in comparison to care as usual, i.e. with or without following guideline recommendations.

In chapter 9, the General discussion, the main findings presented in this thesis are reviewed, and theoretical and methodological considerations and limititations of the studies are discussed. Recommendations for further research, evaluation and implementation of stepped-care strategies for depression are formulated. Also, implications and recommendations of our research findings for clinical practice and health care policy are described.

Part I
Stepped care and depression management

Chapter 2

Stepped care:
concept and aims

Summary

As stepped care is put into practice and evaluated at an increasing scale, its concept continues to evolve. Aim of this chapter is to refine what stepped care is. This chapter describes the stepped-care model and principles of stepped care employed in this thesis, and what a stepped-care approach contributes to depression care.

The aim of stepped care is to simultaneously achieve better treatment outcomes for individual patients (the microperspective), integrated care and a more efficient organisation of care (a mesoperspective), and improved cost-utility of care and equity in allocating care (a macroperspective). In stepped care, these three perspectives are represented. Distinguished in this thesis are stepped-care strategies as treatment strategies versus stepped care as a design for service delivery. Interventions are sequenced from low intensity to high intensity, to support clinical decision making or to coordinate service delivery. Interventions that are lower in intensity are preferred in treatment choices, to avert over-treatment. The course of symptoms and change of needs steer treatment through monitoring of treatment response and periodically evaluating care, to avert under-treatment. Decision support tools for stepped-care strategies, based on the Dutch Multidisciplinary Guideline for Depression, are introduced in this chapter.

Clinical decision making on appropiate treatment strategies and the therapeutic process are key in our stepped-care model. The stepped-care model, as advocated in this thesis, is adaptable in that the sequence of interventions in individual treatment is not fixed or set beforehand. Stepping in and stepping up to follow-up interventions is stratified by the nature, severity and course of symptoms as well as observed treatment outcomes, in consideration of the individual patient's needs and preferences. This stepped-care model implies that stepped-care strategies can be personalised for the patient's profile.

"Everything should be as simple as possible. But not simpler."
Einstein c. 1910

2.1 Stepped care: an old concept, a new future?

In this thesis, we define stepped care as: *care as low in intensity as possible, while as high in intensity as needed, accounting for the nature, duration, severity and course of symptoms (or stages of depression) in an individual treatment plan to achieve treatment goals, by preferring lower intensity interventions over higher intensity interventions when adequate and acceptable, and by adjusting the treatment plan through sequencing interventions (in steps) based on monitoring of treatment response.*

The term *stepped care* is metaphorically used for the order in which treatment alternatives can be sequenced, as well as for each step that needs to be taken for follow-up intervention based on observed treatment outcomes. This methaphor emphasizes the core principles of stepped care. Interventions are sequenced from low intensity to high intensity, in individual treatment strategies and at the organisational mesolevel of service delivery. The course of symptoms and complaints steers individual treatment through monitoring of treatment response and periodically evaluating care. A stepped-care decision tool supports clinical decision making and enables shared decision making by care professionals and patients.

Some twenty years ago, stepped care was introduced in the field of mental health care in the Netherlands. In this period, stepped care was around for many more years in other fields of health care. Stepped care first appeared in the research literature in the late seventies of the 20th century, concerning the treatment of hypertension (Taylor 1977; Sackett 1979). Controlled studies demonstrated the effectiveness of this approach (Moser 2003). Following the examples of stepped care for diabetes mellitus, eating disorders, alcohol dependence and tobacco dependence (Ellis 1984; Fairburn & Peveler 1990; Sobell & Sobell 1995; van den Brink 1996; Hughes 1996; Schippers, Schramade & Walburg 2002), the stepped-

care approach was applied to depression and anxiety disorders (Guscott & Grof 1991; Katon et al. 1995; 1999; Tiemens 1999; Von Korff & Tiemens 2000; Davison 2000; Otto et al. 2000). Stepped care was advocated by the Dutch government as a quality or efficiency enhancing policy for service delivery (Ministerie van VWS 1984; 1998; 2002). The first Dutch empirical study on stepped care for depression (Meeuwissen & van Weeghel 2003a; Meeuwissen et al. 2008) was initiated by Professor Bea Tiemens, one of the early authors on stepped care for depression (Von Korff & Tiemens 2000), and commissioned by the Ministry of Health, Welfare and Sports. With this study on the development, implementation and evaluation of a stepped-care depression programme, which is described in chapter 4, stepped care was introduced in the Dutch mental healthcare sector.

At that time, it was questioned whether stepped care was worthwhile to be implemented in the Netherlands. The value of stepped care for mental health care was debated with viewpoints as divergent as stepped care being already a commonly implemented practice, with nothing new in itself, to stepped care being an utopian care model that would be impossible to implement for both practical and principal reasons.

Much has changed since. Over the years, professionals, patients, healthcare insurers and policy makers began to embrace the concept of stepped care and adapted it in many ways. Stepped care appeared to be of interest from the perspectives of all stakeholders, at micro-, meso- and macrolevel. Stepped care was used as a guiding principle for care professionals in offering appropriate care to patients and formulating treatment alternatives for the patient, for designing service delivery and allocating resources for care, as well as for controlling healthcare expenditure (Haaga 2000; Bower & Gilbody 2005; Andrews 2006; 2007). The number of studies on the implementation and evaluation of stepped care has grown with an increasing rate over the last seven years. Other promising care concepts seem more fashionable in the current Dutch healthcare debate.

Dutch mental health care has been described as a combination of stepped care and matched care (Tiemens 2017). As far as the service delivery system is concerned, stepped care is organised in echelons with an increasing intensity of care: primary care or general practice, with support of the nurse practitioner ('huisartsenzorg inclusief POH-GGZ'), general mental health care ('generalistische basis GGz') in primary care, secondary care or specialised mental health care ('gespecialiseerde GGz'), and highly specialised care ('hoogspecialistische zorg') for a small proportion of patients (Meeuwissen, van Bon et al. 2018).

As the concept continues to evolve, a clear understanding of stepped care can contribute to advancing depression care. The aim of this chapter is, firstly, to describe the concept and aims of stepped care from the micro-, meso- and macroperspective, and the stepped-care model in which these three perspectives are represented, and, secondly, to introduce the decision support tools for stepped-care strategies for depression, that are studied in this thesis.

2.2 The stepped-care model

The promise of stepped care consists of the possibility of making improvements on the micro-, meso- and macrolevel simultaneously. In a model of care based on the principles of stepped care, the micro-, meso- and macroperspectives are combined and aligned. Improvement from one of these perspectives is adding value as viewed from all perspectives (see Figure 1).
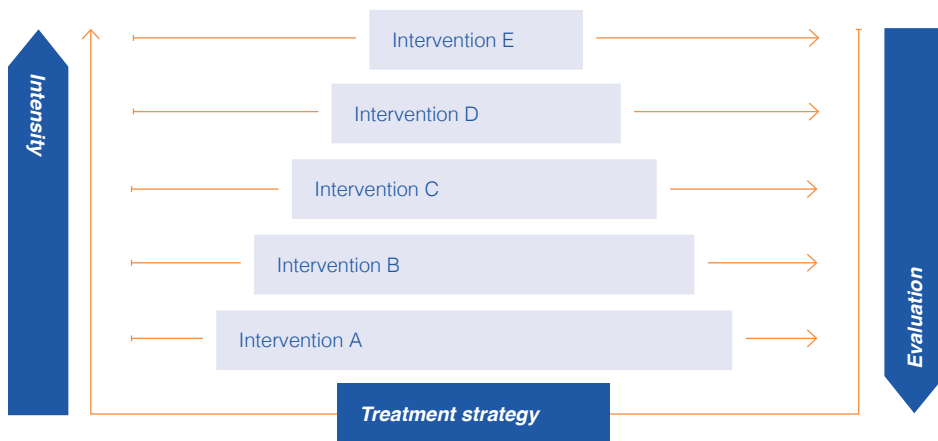
Figure 1 *The stepped-care model (Meeuwissen & Donker 2004, after Sobell & Sobell, 1993)*

In this stepped-care model after Sobell & Sobell (1993), an individual treatment strategy for depression is depicted, from a microperspective. In individual treatment strategies, interventions that are lower in intensity are preferred in treatment choices. Treatment outcomes are monitored proactively and the treatment plan is evaluated periodically. When treatment response is insufficient, the treatment plan is changed by stepping up to a more intensive intervention. Performing stepped-care strategies in the treatment of depression is supported by the availability of a predefined sequence of interventions that are expected to benefit the patient, as well as by explicit criteria for monitoring, evaluating and stepping up. From a mesoperspective, to improve the efficiency of care, interventions are sequenced from low intensity to high intensity. Monitoring and evaluation is integrated into the treatment process in order to improve the efficieny of care. From a macroperspective, the assumption is that fewer patients need the more intensive interventions. More intensive treatment is available for patients who need it. Stepped care in our model consists of six principles that will be covered in the following paragraphs. These principles of stepped care are summarised in Table 1.

1   To achieve individual treatment goals stepped care treatment strategies account for the nature, duration, severity and course of symptoms and complaints

2   In clinical decision making, evidence-based interventions that are lower in intensity are preferred over evidence-based interventions that are higher in intensity when appropriate and acceptable

3   The course of symptoms and complaints steers treatment policy through monitoring of treatment response and periodically evaluating care

4   A stepped-care decision tool supports clinical decision making and enables shared decision making

5   The organisational framework of care fulfills conditions to perform stepped-care treatment strategies (f.e. sequenced care programmes, shared care, monitoring systems, clinical pathways, availibility of interventions throughout the care continuum)

6   Stepped care combines perspectives in aiming for:

– better treatment outcomes for individual patients (microperspective)

– integrated care and a more efficient organisation of care (mesoperspective)

– improved cost-effectiveness of care and equity in allocating care (macroperspective)

Table 1   The six principles of stepped care

2.3 The microperspective: stepped care as a treatment strategy

Stepped care is in the first place a treatment strategy for decision making under uncertainty. At the heart of stepped care lay the ancient medical-ethical principles *in dubio abstine* (when not certain, do not intervene) and *primum non nocere* (at least, do not harm; attributed to Hippocrates circa 400 B.C.) or the awareness that an intervention implies a chance for cure or recovery, but can possibly also harm the patient. Applying these principles requires a stepped-care approach whenever uncertainty exists on what intervention will be most beneficial for the patient, and any time a judgement needs to be made on when an how to intervene.

In this thesis, *a stepped-care strategy* is defined as: *a treatment strategy in which the care professional and patient consider, together, which treatment is most appropiate for the nature, duration, severity and course of symptoms whilst avoiding over-treatment as well as under-treatment, by preferring the least intensive (or least invasive) treatment alternative as the intervention of first choice to reach individual treatment goals, and care professional and patient continuously monitor changes in symptom severity and step up to a more intensive intervention when the current intervention yields insufficient treatment response.* The routinely

monitoring of the severity and course of symptoms and the periodical evaluation of treatment and its outcomes are essential in a stepped-care strategy (Von Korff & Tiemens 2000; Meeuwissen & van Weeghel, 2003a). The strategy of gradually intensifying care as needed is followed until the desired treatment outcomes are achieved (Meeuwissen & van Weeghel 2003a; Davison 2000; Von Korff & Tiemens 2000; Wilson et al. 2000; Donovan & Marlatt 1993). When treatment goals are reached, for example when remission is established, the treatment plan is adjusted serving new treatment goals, such as concerning relapse prevention or functional recovery, by choosing again the least intensive intervention possible, again taking into account the severity and course of symptoms or complaints, and the treatment alternatives to reach these new treatment goals. This may imply stepping back to a less intensive treatment to start with, such as only monitoring or maintenance treatment.

In a stepped-care strategy the initial treatment is not necessarily the absolute least intensive intervention, but the least intensive intervention that is appropriate considering the individual patient's needs, based on the nature, duration, severity and course of symptoms, as well as patient preferences. As thus, it is allowed to start with an intervention that is higher in the hierarchy in which interventions can be ranked according to their intensity (Sobell & Sobell 1995; Abrams et al. 1996; Von Korff & Tiemens 2000; Newman 2000). It is recommended that certain interventions in the hierarchy are skipped for patients when the risk of harmful treatment delay needs to be accounted for, or when adverse effects are expected from less intensive interventions. For example, when experienced treatment failure negatively affects later treatment outcomes, then minimal interventions may not be appropriate (Bower & Gilbody 2005).

As we saw in the introduction of this thesis, matching principles can be applied in stepped care to tailor treatment to patient characteristics as well. However, the extent to which these are expected to moderate treatment outcomes as desired is rather limited (Simon & Perlis 2010). In paragraph 2.5 we will discuss how stepped care relates to person-centred care, as in staging or profiling care.

2.4 Sequencing interventions in stepped-care strategies

To support clinical decision making, interventions that are expected to be effective for a group of patients can be ranked from least to most intensive in a predefined sequence of interventions in a stepped-care model. This sequence of interventions can be based on different values, depending on the perspective one is taking or the benefits that one hopes to reach. The least intensive (or minimal) intervention is, for example, supposed to be the most easy accessible, in a generalistic treatment setting instead of specialty care, requiring the shortest time to deliver, or the least

costly intervention in terms of amount of specialist time required (cf. van Straten et al. 2015; van Straten et al. 2010; Bower & Gilbody 2005; Scogin, Hanson & Welsh 2002; LCGV 2002; Haaga 2000; Tiemens 1999; Donovan & Marlatt 1993; Goldberg & Huxley 1980). These mesoperspectives can complicate ordering the sequence of interventions. How, for example, do you weigh these different values? When the micro- and mesoperspective are tangled, how do you balance the mesoperspective with patient values? In the therapeutic process, from the microperspective, the least intensive intervention is considered to be the least intensive for the patient and not necessarily the absolute least intensive intervention. It is of shorter duration or requiring less time, or is less restrictive, invasive or intruding in the patient's life or body (Sobell & Sobell 2000). In line with this, a minimal intervention is not per se the absolute least intensive intervention.

In the tradition of evidence-based mental health (Sackett et al. 2000; Straus et al. 2010), in sequencing the interventions, the recommendations in evidence-based clinical guidelines are followed (e.g. Spijker et al. 2013; Spijker et al. 2010; van Weel-Baumgarten et al. 2012; National Collaborating Centre for Mental Health 2009; New Zealand Guidelines Group 2008). Evidence-based mental health care, as reflected in clinical practice guidelines, is in this thesis the main determinant for establishing the sequence of interventions. When evidence for interventions being more (cost)effective than other interventions for the particular patient group is not available, these alternative treatment options are to be placed on the same level in the step-order of interventions. Treatment choice within this level is then, resulting from shared decision making, ususaly depending on, for example, the results of earlier treatment or the patient's preferences.

Sequencing of interventions in establishing or adjusting an individual treatment plan requires that the interventions are well-chosen. This implies that we need to explicitly define the clinical decision to be made and the individual treatment goals to achieve. We must consider the alternative interventions for the patient, and how these may change subsequent health states, and the respective probabilities that these will result from the interventions. In this process it is important to mind patient values and trade-offs (such as between desired and undesired outcomes, short-term and long-term benefits, gains and losses or sacrifices to be made), and to balance the benefits and harms of these alternative interventions (Hunink et al. 2001). In this sense, stepped care fits well with shared decision making by patient and care professional (Von Korff & Tiemens 2000; Kates et al. 1997). In shared decision making, treatment responsibilities concern psychoeducation and involving and enabling the patient to participate in informed decision making (Elwyn et al. 2012). What stepped care adds to shared decision making is the responsibility to choose care that is appropriate and acceptable for the patient while avoiding over-treatment as well as under-treatment.

Furthermore, in stepped care the care professional and patient jointly monitor the course of symptoms and complaints and evaluate and adjust treatment policy accordingly. In chapter 3 we will discuss how stepped care relates to routine

outcome monitoring that is integrated in the therapeutic process. In monitoring outcomes and evaluating treatment it can become clear that either patient's compliance to the treatment policy, or the care professional's adherence to evidence-based guidelines are not optimal and need to be improved in order to reach treatment goals (Delgadillo et al. 2017; van Fenema 2016; Von Korff & Tiemens 2000; Donker & Meeuwissen 1998).

Sequencing of interventions requires that criteria for stepping up are made explicit. These evaluation criteria for whether or not to step up to a subsequent intervention need to be based on the valid measurement of symptom improvement at timepoints when improvements can be expected with the given intervention.

To support care professionals, and their patients, in (shared) decision making on sequencing interventions and stepping up when needed, decision support tools can be developed.

2.5 Decision support tools for stepped-care strategies

With each decision in a stepped-care strategy, it is of main importance to prevent over-treatment as well as under-treatment. The stepped-care sequence of interventions and accompanying evaluation criteria can be summarised in decision support tools (heuristics), such as a treatment algorithm, making explicit the information that is most relevant for the decision making. These decision support tools are not fixed and do not reflect a strict order that for all patients and in all cases needs to be followed per se (see paragraph 2.3). Rather, they reflect the sequence in which care professionals and patients can consider the treatment alternatives, as well as the criteria for stepping up. This way, stepped-care decision support tools provide in the need for individually tailoring. Treatment response and the course of symptoms and complaints are being monitored and periodically evaluated by explicit criteria. The observed data feed into the stepped-care decision tool which informs clinical decision making on stepped-care strategies. In stepped-care decision support tools, the treatment alternatives summarised for each decision point in the therapeutic process are ordered from low-intensity to high-intensity.

Evidence-based clinical guidelines for depression that provide the evidence base for the sequence of interventions and stepping-up criteria are available, integrating best-evidence and expert opinions (Spijker et al. 2013; Spijker et al. 2010; van Weel-Baumgarten et al. 2012; National Collaborating Centre for Mental Health 2009; New Zealand Guidelines Group 2008). The stepped-care algorithm for diagnostics and treatment of depression in chapter 4 is based on the at that time available Dutch Multidisciplinary Guideline for Depression (CBO/Trimbos Institute 2005). This clinical guideline is being kept up to date with best evidence, following

the method of evidence-based guideline development (Assendelft & Scholten 2003; Regieraad Kwaliteit van Zorg 2012) and involving a large number of professional associations and patient participation.

For the current revised Dutch Multidisciplinary Guideline for Depression (Third revision, Spijker et al. 2013), stepped-care algorithms were developed to support care professionals in sequential treatment strategies guided by outcome monitoring. These stepped-care decision tools supply the evidence for decision making: evidence-based treatment options and the sequence in which the interventions need to be considered are in line with current evidence on appropriate and acceptable depression care. To support clinical decision making under uncertainty about the individual prognosis, the stepped-care algorithms offer a heuristic for a timely and adequate treatment policy. Taking account of the nature, duration, severity and course of symptoms, the stepped-care algorithms provide clinically relevant evaluation criteria and time indications based on which clinical decisions on treatment policy can be made. According to the stepped-care algorithms, outcomes are monitored, and treatment evaluation results in stepping up to more intensive follow-up interventions when needed.

To achieve treatment goals while avoiding unwanted consequences, the stepped-care algorithms make explicit the treatment steps and evaluation criteria for respectively: i) Mild depression, single episode, with a duration shorter than three months; ii) Mild depression, with a single episode longer than three months or a recurrent episode; iii) Moderate and severe depression, single episode; iv) Moderate and severe depression, recurrent episode. According to the stepped-care algorithms, the basic interventions (i.e. i. psychoeducation, ii. actively monitoring of symptoms and complaints, and iii. structuring of the day), are offered to all patients. In single or recurrent mild episodes of MDD with a duration of at least three months (when the basic interventions alone or followed by either problem solving therapy or brief therapy) did not reach sufficient recovery, first psychotherapy (i.e. cognitive behavioural therapy, behavioural therapy or interpersonal therapy) is indicated. When this does not lead to improvement after 4 months, either switching within psychotherapy or switching to pharmacotherapy is indicated. For single episodes of moderate and severe MDD, either psychotherapy (i.e. cognitive behavioural therapy or interpersonal therapy) or pharmacotherapy is immediately indicated. In recurrent moderate and severe episodes of MDD, the guideline recommends to continue treatment with either psychotherapy or a combination therapy of psychotherapy and pharmacotherapy (not pharmacotherapy only), because of the long-term prophylactic effect of psychological intervention protecting against recurrences.

In shared decision making by means of the stepped-care algorithms, also treatment history of previous experience or outcomes of earlier treatment, comorbidity (somatic, interpersonal or psychosocial), other expected treatment effects (for example on sleeping), expected or occurring side effects or interactions,

treatment outcomes in firstdegree family members, personal history, personal situation, or other patient characteristics, combined with patient preferences, can determine appropiate care (Meeuwissen, van Bon et al. 2018).

A cost-utility analysis of the stepped-care algorithms is decribed in chapter 8.

2.6 The mesoperspective: stepped-care service delivery

At the mesolevel the conditions to perform stepped-care treatment strategies are shaped. From the mesoperspective, the aim of stepped care is greater quality and efficiency in service delivery through integrated care.

In accordance with evidence-based mental health care, the unit of sequencing is (as we saw in paragraph 2.4) the *intervention* (or the content of care), so that the mesoperspective is in line with the microperspective from which treatment policy is considered. In differentiating only the echelon of care, such as generalised (mental) health care or specialty care, arguments of cost containment, cost control or the balance of relationships of stakeholders involved often become predominant (Boot 2015; Boot & Knapen 2004; Meijer & Verhaak 2004; Rijk et al. 1999; van Lieshout & Stoelinga 1988; Schnabel 1985).

One assumption is that allocating low-intensity interventions will result in greater efficiency of care (Bower & Gilbody 2005). The organisational framework in which care professionals operate can mediate macrolevel influences and create effects on the microlevel (Dopfer, Foster & Potts 2004). Our assumption is, secondly, that integrating care processes in such a way that the conditions for care professionals to perform stepped-care treatment strategies are improved, results in efficiency in service delivery. By integrating care processes, uncertainty in the therapeutic process can be reduced through stepped care. Examples of improving the conditions for the therapeutic process are: the implementation of evidence-based clinical practice guidelines; availability of interventions throughout the care continuum, decision support tools (heuristics), methods for routine outcome monitoring, electronic patient information systems with self-management support; and indicating casemanagement to improve compliance and multidisciplinary care coordination (Von Korff, Katon, Unützer, Wells & Wagner 2001).

In the Netherlands, since the 1990s most mental healthcare services organised their care in so-called care programmes (van Fenema et al. 2016; van Wamel et al. 2005; Schene & Verburg 1999). Within care programmes the principles of stepped care can be applied (Meeuwissen 2001). More recently, clinical pathways are implemented to ensure the continuity of care provided by different care providers in different settings (van Splunteren et al. 2014). For patients with a long-term need for care, continuously or episodic, a number of different care professionals

is involved. With the development and implementation of care pathways for categories of patients it is attempted to offer integrated care. However, stepped-care strategies of gradually intensifying care and steering the treatment policy based on continous outcome monitoring, are ususally not fully integrated yet in these developments.

The stepped-care sequence of interventions can cover the whole continuum of care from prevention, recognition, acute and long-term treatment to aftercare, relapse prevention, individual reintegration, and establishing full recovery. For stepped-care service delivery that unites care from different settings, important preconditions are transparency of the treatment options and multidisciplinary care coordination by means of shared care or collaborative care. Shared care and collaborative care can be successfully integrated into a stepped-care approach (Smith, Cousins, Clyne, Allwright & Dowd 2017; van Orden 2017; Unützer & Park 2012; van der Feltz-Cornelis et al. 2010; Ell et al. 2010; Richards & Suckling 2009; Katon et al. 2002; Simon et al. 2001; Katon et al. 1999).

In the United Kingdom, a nationwide stepped-care delivery system, the 'Improving Access to Psychological Therapies' (IAPT) services, is implemented to improve access to evidence-based psychotherapy based on the NICE guideline (Clark et al. 2017; Firth, Barkham, Kellett & Saxon 2015; Richards 2012; Richards & Suckling 2009; Clark 2011; Clark et al. 2009). In the Netherlands, to improve the uptake of the Dutch Multidisciplinary Guideline for Depression in daily practice, as well as to improve multidisciplinary collaboration between mental healthcare professionals, a 2-step stepped-care model was implemented with the Institute for Health Care Improvement's Breakthrough method. The study evaluated whether this stepped-care model leads to quality improvement in depression care (Franx et al. 2012; 2009, see chapter 5). These initiatives demonstrated that translation of the seemingly simple principles of stepped care into daily practice turned out not to be straightforward since various obstacles to its full implementation were encountered (Chan & Adams 2014; Hermens et al. 2014; Sinnema et al. 2013; Franx et al. 2012; Sinnema et al. 2011; Richards et al. 2012; Clark 2011; Clark et al. 2009), as will be discussed in chapter 5.

2.7 Aims of stepped care from a macroperspective

From the macroperspective, stepped care is a population health approach to patient care with the aim of improved cost-effectiveness of care and equity in the allocation of care.

With stepped care a more cost-effective allocation of scarce resources is expected (Bosmans, van Schaik, de Bruijne, van Hout, van Marwijk, van Tulder & Stalman

2008; Bower & Gilbody 2005; Davison 2000; Haaga 2000), because stepped care is assumed to result in a greater health gain than care as usual within the same or a lower healthcare budget. Several studies on the cost-effectiveness of stepped care are in favour of stepped care, showing that cost-effectiveness is at least equal to care as usual, or the higher costs are related to greater effectiveness (Simon et al. 2001; Katon et al. 2005; Araya et al. 2006; Simon et al. 2007; van 't Veer-Tazelaar et al. 2010).

In improving the cost-effectiveness of depression care, a broad macroperspective on stepped care considers equity through distributing health among the population. Care improvements on the mesolevel in part of the care continuum or for some groups of patients that would entail adverse effects on other parts or for other patients, are to be avoided. Therefore, it is important that the three perspectives, micro-, meso- and macroperspective, are all aligned. In this way, by means of a better allocation of scarce resources through stepped care, more patients are expected to receive better care.

Randomised trials on stepped care in depression are performed in populations where health resources are scarce in an absolute manner and access to health care is limited or not equally distributed over all subgroups of the population. In studies of Araya et al. (2003; Siskind et al. 2010) the effectiveness of a stepped-care programme with usual care in primary-care management of depression was studied in low-income women in Santiago, Chile. Women with major depression responded well to the structured stepped-care treatment programme consisting of a psychoeducational group intervention, systematic monitoring of clinical progress, and a pharmacotherapy programme for patients with severe or persistent depression. The authors conclude that socially disadvantaged patients might gain the most from systematic improvements in treatment of depression. In the studies by Patel et al. (2010; Patel, Chowdhary, Rahman & Verdeli 2011; Patel, Weiss et al. 2011) a collaborative stepped-care intervention offered case management and psychosocial interventions, provided by a trained lay health counsellor, supplemented by antidepressant drugs by the primary care physician and supervision by a mental health specialist. In public facility attenders, a strong effect on recovery at 6 months was found for patients with ICD-10-confirmed common mental disorders in the intervention group.

2.8 Arguments pro and con stepped care

In lack of conclusive evidence, it has been questioned whether stepped care is worth the effort of further developments and implementation. Criticism stemming from principal objections we discuss here. In the General discussion of this thesis (chapter 9) we will return to this issue.

1 *Establishing the sequence of interventions is impossible, due to an insufficient evidence-base.* Here problem and solution are mixed up. The stepped-care approach is actually seeking a pragmatic way to offer adequate care and the best fitting care when evidence on the best match between patient and treatment is lacking. Also when evidence is not strong, a clinical decision must be made. Stepped care lays out the criteria based on which this decision in uncertainty can be made. When research generates more knowledge on which treatment works best for which patient, these findings can be integrated into a stepped-care delivery system and in stepped-care decision support tools. Stepped-care decision support tools may in the end be replaced by a matched-care algorithm or protocol. However, this is not yet at stake and in the meanwile the pragmatic approach with stepped-care strategies seems fruitful (Simon & Perlis 2010; Wilson, Vitousek & Loeb 2000; Ilardi & Craighead 1994).

2 *The sequence of interventions is too rigid.* In practice, other aspects define appropriate care and, according to this reasoning, too tight recommendations will not be followed. However, in our definition, it is not inherent to stepped care that in all cases the same step order is followed or that all the interventions of all treatment levels need to be tried before stepping up is possible. Moreover, when there is good reason to directly start with a more intensive treatment, this is recommended, also in a stepped-care treatment strategy (Spijker et al. 2013; 2010). A lower intensity intervention is only indicated when there is no need for a more intensive intervention, as described in paragraph 2.4.

3 *It is more effective to start with a more intensive intervention so as not to lose time.* This is supposed to be true for some but not all patients. Apart from the argument that over-treatment can be harmful to the patient, this is also a matter of probabilistic outcome assessment. The objection implies that a majority of patients does not reach treatment goals with a less intensive treatment and that a majority in the end needs more intensive treatment. In other words: that the likelihood of under-treatment is higher than the likelihood of over-treatment. However, for this argument is no proof. On the contrary, in many cases of less severe depression, a low-intensity intervention appears to yield positive outcomes (Spijker et al. 2013; 2002). We subscribe to the importance of recognising patients who will not benefit from a low-intensity intervention or for whom treatment delay can cause harm. In those cases, the stepped-care treatment strategy needs to start with a more intensive intervention.

4 *Cheaper interventions are always preferred over more expensive interventions.* From the previous, it may be clear that always preferring cheaper interventions is not what is advocated with stepped care in this thesis. Certainly, it is assumed that since less over-treatment will take place, stepped care may result in greater health gains for more patients than care as usual, also in terms of cost-effectiveness. Improved cost-effectiveness and quality of care against equal or lower costs of care can also bring around equity of care: by means of a better allocation of scarce

resources patients receive better care, while in addition more patients receive better care.

2.9 Effectiveness of stepped care

Various elements of stepped care are developed, implemented and evaluated in mental health care on an increasing scale, although often not yet covering the whole concept of stepped care. Studies on the clinical effectiveness of stepped care in depressed patients are summarised in two systematic reviews (van Straten et al. 2015; Firth, Barkham & Kellett 2015) with different inclusion criteria (regarding age group, percentage of patients with MDD in the sample, comorbidity, operationalisation of stepped care, study design) but 6 overlapping studies (Araya et. 2003; Davidson et al. 2010; Ell et al. 2008; 2010; Patel et al. 2010; Seekles et al. 2011). In both reviews, stepping up to a subsequent intervention had to be based on a systematic clinical evaluation with predefined criteria. Both reviews found small positive effects on depression outcomes, showing that stepped-care interventions for depression are at least as effective as usual care, although current evidence is limited. In the Van Straten et al. study, 14 studies on the prevention and treatment of depression were included (Apil et al. 2012; Araya et al. 2003; Bot et al. 2010; Davidson et al. 2010; 2013; Dozeman et al. 2012; Ell et al. 2008; 2010; Huijbregts et al. 2013; Katon et al. 2004; Patel et al. 2010; Seekles et al. 2011; Unützer et al. 2002; van 't Veer-Tazelaar et al. 2009). All effect sizes included in the meta-analysis (Araya et al. 2003; Davidson et al. 2010 2013; Ell et al. 2008; 2010; Huijbregts et al. 2013; Katon et al. 2004; Patel et al. 2010; Seekles et al. 2011; Unützer et al. 2002) were significantly in favour of stepped care. At 6-month follow-up, a Cohen's d of 0.34 (95% confidence interval 0.20-0.48; k=10; n=4580) was observed.

In the Firth et al. study, 11 randomised trials (Araya et al. 2003; Davidson et al. 2010; Dwight-Johnson et al. 2005; Ell et al. 2008; 2010; 2011; Kay-Lambkin et al. 2010; Patel et al. 2010; 2011; Seekles et al. 2011; van Straten et al. 2006) and 3 studies without a control group were included (Clark et al. 2009; Franx et al. 2009; Richards & Borglin 2011). The median comparative Cohen's d effect size estimate was 0.41 (interquartile intervals 0.25 and 0.45; k=5 studies; n=1843) (Araya et al. 2003; Davidson et al. 2010; Ell et al. 2008; Patel et al. 2010; Seekles et al. 2011). The median odds ratio for recovery was 1.31 (interquartile intervals of 1.05 and 1.66; k=7 studies; n=2959), indicating that stepped care was superior to treatment as usual (Araya et al. 2003; Ell et al. 2008; 2010; 2011; Patel et al. 2010; 2011; Seekles et al. 2011; van Straten et al. 2006). Stepped care showed recovery rates, defined as patients no longer meeting clinical criteria for the specific outcome measure, ranging between 40% and 60% and treatment response rates, defined

as a 50% decrease in symptom severity, approximating 60% of the patients (Firth, Barkham & Kellett 2014). Both reviews show considerable clinical heterogeneity (baseline severity, age, comorbidity) as well as methodological heterogeneity (depression criteria, population and clinical samples, setting, control condition) in the included studies. Also, the treatment steps, the number and duration of these steps, criteria for stepping up and professionals involved in the stepped-care interventions vary considerably, as noted by the researchers.

With the effectiveness studies and systematic reviews on patient outcomes, the evidence-base on stepped-care interventions in depression is growing rapidly. Stepped-care interventions are slightly superior to usual care, but the effect sizes are small. The cost-effectiveness is at least equal to care as usual, or higher costs are related to greater clinical effectiveness. Because of the heterogeneity of the populations being studied (baseline severity, age, comorbidity) and methodological considerations (varying depression criteria, population and clinical samples, setting, control condition), the evidence on the effectiveness of stepped care in patients with major depression is still rather limited, as concluded by the reviewers. Also, the stepped-care interventions are highly variable with varying treatment steps, number and duration of these steps, criteria for stepping up and professionals involved. It remains unclear what the active ingredients in these interventions are, accounting for the nature, severity and duration of the depression symptoms, or the age and comorbidity of the patient.

In many studies, recommended (relatively low-intensive) interventions in line with evidence-based guideline recommendations are evaluated as first treatment steps. However, in none of these studies the sequence of intervention steps and the criteria to step up are completely in line with the current evidence-based guidelines that recommend stepped-care strategies. In addition, a complete sequence of treatment steps covering evidence-based guideline recommendatios has not yet been studied. In general, whereas evidence-based guidelines recommended to choose from more treatment alternatives or to differentiate treatment choice depending on severity and duration, the intervention steps in the studies seem more fixed and more limited than according to current guidelines.

For the evaluation of stepped care it is again important to distinguish the micro-, meso-, and macroperspective. More research is needed on the effectiveness of individual stepped-care strategies as well as on the efficiency of stepped care delivery systems. Also, specifically the cost-effectiveness of stepped-care decision support tools for treating depression compared to care as usual is still unknown.

2.10 Preliminary conclusions

Stepped-care algorithms in the Dutch Multidisciplinary Guideline for Depression provide in tailoring to the severity, duration and course of the depressive episode of individual patients. According to these algorithms, treatment is the least intensive possible whilst the most intensive needed to obtain the best outcome for the patient. Initial and subsequent interventions are started not earlier or more intensely than necessary, not later or less intensely than needed.

Various elements of stepped care are implemented in depression care, albeit not in an integrated way. It seems promising to develop and implement stepped-care strategies, at the microlevel, and to organise care accordingly, at the mesolevel. When the three perspectives are aligned, better treatment outcomes for individual patients and better treatment outcomes for more patients in the population are expected. To perform effective individual treatment strategies, the conditions for care professionals to perform well need to be fulfilled on the mesolevel. Macrolevel influences to improve cost-effectiveness of care and equity in allocating care can be mediated by a stepped-care delivery system.

Stepped-care service delivery is evaluated in mental health care on an increasing scale and the results on effectiveness are consistently in favour of stepped care. In studying stepped care, it is important to distinguish individual stepped-care treatment strategies from stepped-care delivery systems and the accompanying aims that are relevant from the different perspectives.

Chapter 3
Management of depression care:
concept and aims

Parts of this chapter have been published as:

Meeuwissen, J. (Ed.) (2008). *Disease management in mental health care.*
[Disease management in de geestelijke gezondheidszorg.]
Utrecht: Trimbos-instituut.

Meeuwissen, J., Sinnema, H., Munthingh, A. (2011). *Organization of care*.
[Organisatie van zorg.] In: Balkom, A.J.L.M. van, Oosterbaan, D., Visser, S.,
Vliet, I.M. van (Red.). Handboek Angststoornissen. Utrecht: De Tijdstroom.

Summary

Aiming for improvement in quality and efficiency of care processes at the mesolevel of service delivery, chronic care management provides in a steering principle based on measurable outcomes. The principles of stepped care can strengthen a chronic care management approach and add value to chronic care management, as this chapter describes.

Self-management support, delivery system design, decision support, and clinical information systems, are important components in depression care management according to the Chronic Care Model. The jointly, by patients and care professionals, and routinely monitoring and evaluating of treatment outcomes, integrated in treatment and self-management support, is one of the principles of stepped care. Coordination of integrated care processes across the care continuum reflects the need for delivery system design. Structuring evidence-based interventions in a stepped-care service delivery, with a sequence of steps of increasing intensity, fits well into this second component. Clinical information systems that provide in organising timely and relevant individual and aggregated patient and population data to facilitate efficient and effective care, are a third element in the Chronic Care Model. Individual treatment strategies are adjusted on the basis of the monitoring and evaluating of treatment outcomes in stepped-care strategies, also within a chronic care management approach. Care processes are delineated on the basis of evidence-based clinical guidelines and standards of care, according to the fourth component. Their use and embeddedness in clinical practice is promoted by chronic care management strategies and care coordination with the professionals involved. Decision support concerns a principle of stepped-care: a stepped-care decision tool can support clinical decision making and enable shared decision making.

The routinely monitoring and evaluating of care processes by outcomes management is fundamental in chronic care management. Clinical management following the principles of stepped care is highly compatible with it. The paramount focus in monitoring and evaluating within healthcare organisations should be on individual treatment strategies and the outcomes measured should be of relevance to the patient in order to create value-based health care, as we describe.

Proactive interactions between patients and care professionals are pivotal in depression management. A depression care management process model is described in which feedback loops operate between the patient level (microperspective), the care process level of service delivery (mesoperspective) and the care policy macrolevel.

"Anticipate the difficult by managing the easy."
Lao Tzu, c. 604-c.531 B.C., Tao-te Ching

3.1 Management of depression care: chronic care management

Care improvement strategies that rely on the Chronic Care Model (Wagner et al. 1996; 2001; WHO 2002; Bodenheimer 2003; Coleman et al. 2009) aim for improvement in quality and efficiency of care processes at the mesolevel of care that results in improved effectiveness of individual treatments: *offering the right care at the right place at the right time* (Wagner et al. 2005; Ellrodt et al. 1997). In the Netherlands, chronic care management approaches are implemented and evaluated in chronically ill (Lemmens, Rutten-van Mölken, Cramm, Huijsman, Bal, Nieboer 2011; Steuten 2006), especially in COPD care (Lemmens 2009), care for heart failure (Drewes 2012) and diabetes care (Elissen 2013).

Chronic care management is, just as stepped care, a coordinated approach to patient care with the aim of delivering care as efficient as possible with the best optimum of results. Depression care management in a chronic care management approach is, just as stepped care, covering the whole care continuum while aiming to prevent exarcebation of symptoms in chronic conditions at all stages or states of depression. Depression care management that includes timely recognition and subsequent careful monitoring of symptoms can help to improve both the healthcare delivery system and individual patient health gains and treatment outcomes.

This chapter addresses how the management of depression care benefits from a chronic care management approach, and describes how care improvement strategies can be pursued to ensure quality and efficiency gains in depression care. We discuss how the principles of stepped care fit well into depression care management. We describe the components of the Chronic Care Model and how a stepped-care approach can strengthen depression care management adding value to these components. In chapter 7, chronic care management strategies for depression management including these components are included in our

systematic review, and assessed to explain their contribution to improvement in care processes and treatment outcomes.

3.2 Chronic care management

In a chronic care management strategy, disease control and care management are based on measurable outcomes. In comparison to stepped-care strategies, that are steered by individual treatment outcomes, provided is a steering principle based on measurable outcomes at the mesolevel of service delivery, possibly but not necessarily on top of treatment outcomes at the patient level. In the United States of America, were the initiatives started for profit, employers and health plans outsource disease management services to commercial vendors or health maintenance organisations (HMOs) (Matheson et al. 2006; Ellwood 1988). Thus, these third parties are steering the care processes (Mos & Schreuder 1999). In comparison, in Europe chronic care management is more integrated in traditional healthcare delivery (Elissen 2013; Schrijvers 2006). However, in Europe the insurance company is involved as a third party that can steer the choices of patients and the decision making process of healthcare professionals (Zorgverzekeraars Nederland 1998). In the Netherlands, contracting of healthcare providers by insurance companies on quality is inserted as the vehicle to improve the quality of care and sustain affordability of care (VWS 2015; VWS 2006). In the contracting phase, insurance companies are allowed to enclose a set of quality requirements concerning, for example, applying clinical practice guidelines or restricting waiting lists.

Chronic care management is highly compatible with the policies of the Dutch government (VWS 2015; VWS 2008; Boot 2015; 2013), like other European governments, increasingly constrained to control macro-costs and to safeguard equal access to health care. The various parties involved, subject to market forces and regulations, have been apportioned the following roles: patients are to be critical consumers who make responsible choices from the available care; health insurers are to compete on price, service or quality through cost-effective procurement; healthcare providers are to deliver efficient, good-quality care. The government sees its own task as safeguarding the quality, accessibility and affordability of health care by promoting competition, transparency and public control (VWS 2015; 2004).

On the supply side, conflicting interests between various professional groups and controversies about task allocation and demarcation have previously inhibited quality-based competition as well as the development of integrated care arrangements. In the positive scenario, health insurers will join hands with professionals to make decisions about healthcare provision. Health insurers can

thus play a constructive role in the further development of high-quality, efficient care. This requires that they operate from a shared vision on care and that they purchase integrated seamless care along the care continuum.

Transparency about the care services delivered, as well as about the care processes, is essential to a healthy market. Chronic care management can provide that transparency (Baan 2015; Wagner et al. 2001).

3.3 The Chronic Care Model

The evidence-based framework of the Chronic Care Model (CCM) (Wagner 1998; 2001; Coleman et al. 2009) was adapted by the World Health Organization as the Innovative Care for Chronic Conditions Framework (WHO 2002). The Chronic Care Model is a synthesis of the best available evidence on system changes as a guide to quality improvement and disease management activities. The Chronic Care Model has proven feasible and acceptable in helping healthcare organisations in quality improvement (Wagner et al. 2001). Redesigning health care using the Chronic Care Model can result in improved patient care and better health outcomes (van Leijen-Zeelenberg et al. 2016; Coleman et al. 2009).

A population healthcare approach is reflected in the Chronic Care Model by representing the health system as well as the community as a resource for high-quality chronic care: the health system by creating a culture, organisation, and mechanisms that promote safe, high quality care; and the community by mobilising community resources to meet the needs of people with long-term conditions. Proactive interactions between patients and professionals are pivotal in the Chronic Care Model (Wagner et al. 2001).

Other elements in the Chronic Care Model are the components of self-management support, delivery system design, decision support and clinical information systems. Well-designed interactions between the practice team and patients produce optimal patient outcomes, according to the Chronic Care Model. The more comprehensive and coherently operating the components of chronic care management are, the more likely it is to be succesul (Coleman et al. 2009; Wagner et al. 2001).

3.4 Self-management support and stepped care

Self-management support (SMS) concerns empowering and preparing individuals to manage their health and health care (Wagner et al. 2001). It helps to activate

and inform patients and their families to cope with the chronic illness and to improve the confidence and skills in managing their condition. An active patient role supported by psychoeducation and self-management strategies is vital in chronic care management. Patients are encouraged to comply with treatment and lifestyle or behavioural change recommendations, and to employ self-management or self-control techniques. This cognitive and behavioural change can have positive effects on the course of depression, improve the outcome of treatment and reduce risks of chronicity, complications or comorbidity (VWS 2008; WHO 2008; 2004; Wagner 1998). Self-management support therefore adds substantial value to the therapeutic process and can be realised as follows.

At the start of treatment, the care professional and patient establish together the individual treatment goals as well as self-management goals and discuss the available treatment options and self-management strategies. The care professional motivates the patient to become committed to the treatment. Care professional and patient take a step in the treatment, they evaluate that step on the basis of results of the monitoring of symptoms and complaints, they identify barriers to reaching treatment or self-management goals, and discuss a plan to overcome these barriers or take the next step in treatment. The care professional employs methods to promote treatment compliance, steadily motivates the patient to provide active feedback about the treatment, and uses that feedback to review the previously agreed treatment plan together with the patient. This jointly and routinely monitoring and evaluating care, integrated in the therapeutic proces, is one of the principles of stepped care, as we saw in chapter 2.

3.5 Delivery system design and stepped care

A second element of the Chronic Care Model is delivery system design (DSD) for efficiently delivering effective care and self-management support (Wagner et al. 2001).

The fluctuating course of depression requires coordination of integrated care processes across the care continuum. To ensure continuity of care, it is necessary to plan and coordinate the integrated care process of all care professionals involved that may need to provide care during the cours e of depression: from prevention, early detection and acute treatment, to maintenance treatment, aftercare, reintegration, and relapse prevention. This may imply task reallocations through site-of-care substitution, for instance within a collaborative care or shared care model (Katon et al. 1995; Katon et al. 1999; Kates et al. 1997). The quality and efficiency benefits lie in a clear demarcation of tasks and in explicit agreements between services and between patients and providers about treatment and decision making responsibilities (Bijl et al. 2004; Von Korff et al. 1997).

Chronic care management also benefits from effective improvement strategies or change strategies and strong leadership from the health organisation, appropriate incentives, ready acces to nurse case managers or other care professionals that assist in self-management support and disease control, and innovations in the scheduling of visits and follow-up (Wagner et al. 2001). Besides telephone support, e-mental health tools can support care processes (Riper et al. 2008). A key issue is to avoid suboptimisation, whereby improvements in parts of the care continuum have adverse effects on other parts.

In a stepped-care service delivery design (as described in chapter 2), evidence-based interventions that are allocated across the care continuum are structured in a sequence of steps of increasing intensity, so as to enable timely intensification of treatment in keeping with the nature, severity and progression of symptoms at all stages or states of depression.

3.6 Clinical information systems and stepped care

Clinical information systems (CIS) that provide in organising timely and relevant patient and population data to facilitate efficient and effective care, are a third element in the CCM model (Wagner et al. 2001).

From a public health viewpoint, chronic care management involves the prevention of new cases combined with the long-term monitoring and management of chronic cases. Population data such as the prevalence, incidence and clinical course of depression, as well as the associated costs of care, input strategies for timely detection of new cases, and prevention of exacerbation or relapse during treatment, can enable timely, appropriate treatment of populations located both inside and outside clinical settings. Focal points of attention can minimise complications and comorbid problems (secondary prevention); prevent exacerbation of disease-related and concomitant problems (tertiary prevention); prevent post-recovery relapse; provide primary prevention aimed at avoiding the onset of disorder; and perform active case-finding, including the engagement of employers and company doctors in prevention efforts.

Collecting, summarising and reviewing individual or aggregated patient data facilitates care when criticial information about each patient, and the performance and results of important aspects of care, enables care teams to call in patients with specific needs, deliver planned care, or implement reminder systems (Wagner et al. 2001).

Through monitoring of treatment response and periodically evaluating care, the progress of symptoms helps to optimise treatment in a stepped-care strategy (as described in chapter 2). Individual treatment strategies undergo adjustment on the

basis of the monitoring and evaluating of treatment outcomes; if necessary, this entails stepping up to more intensive intervention. As thus stepped-care strategies can be performed within a chronic care management approach.

3.7 Decision support and stepped care

Decision support (DS) can promote care that is consistent with research evidence, professional experience, and patient preferences (Wagner et al. 2001).

Care processes can be delineated on the basis of evidence-based clinical practice guidelines and standards of care. The use and embeddedness of these quality standards in clinical practice is promoted by chronic care management strategies and care coordination with the professionals involved. Decision support tools are designed to aid the decision making process in setting out individual treatment strategies (see also paragraph 2.5). This can improve the quality and efficiency of professional action and the transparency of care provision, as well as discourage unwarranted practice variations.

The principles of stepped care are reflected in evidence-based clinical guidelines (Spijker et al. 2013; Spijker et al. 2010; van Weel-Baumgarten et al. 2012; National Collaborating Centre for Mental Health 2009; New Zealand Guidelines Group 2008). The treatment alternatives in these guidelines that are proposed in the clinical encounter can represent the whole care continuum. The stepped care sequence of interventions and accompanying evaluation criteria can be summarised in decision support tools, as we saw in chapter 2. Decision support concerns a principle of stepped care: a stepped-care decision tool supports clinical decision making and enables shared decision making.

3.8 Outcomes management and clinical management

Chronic care management can unite outcomes management and clinical management in depression care (Ellwood 2001; Eichert & Patterson 1997; Epstein & Sherwood 1996). Outcomes management is conducted in a process of continuous quality and efficiency improvement (Walburg 2003). The routinely monitoring and evaluating of care processes in order to improve the clinical outcomes of those processes is fundamental. Clinical management, by making timely adjustments to individual treatment strategies, discussing treatment results with patients and with other professionals involved, and making subsequent adjustments to treatment plans, is not a universal property of chronic care

management nor of outcomes management. Yet, this principle of stepped care can be an added value to it. The monitoring and evaluation of the clinical outcomes of individual treatment strategies (clinical management), and of (outcome and process indicators of) care processes (outcomes management), delivers feedback information that can be processed into aggregated management data for use in communication with service partners. This may facilitate cooperative agreements on consultation and referral, care contracting, the fulfillment of record-keeping requirements and performance agreements, and the clinical benchmarking of healthcare services.

Monitoring and evaluating outcomes can provide patient-level and service delivery-level feedback data. These data can be used to evaluate and improve both clinical outcomes and healthcare service delivery. The management of care processes at the organisational level, can lead to shaping the conditions for improving the primary processes of diagnostics and treatment. Care improvement can be reached through the systematic measuring and evaluation of treatment that resulted in certain outcomes and adjust meso-level care processes accordingly, followed by new measurements and evaluation (Walburg 2003). Clinical management, through the timely adjustment of individual treatment policy based on observed outcomes and discussing these with the patient, with an active rol of both care professionals and patients, fits wel with this.

Benchmarked data and other information are also communicated to third parties as needed for public control, performance indicators, routine outome measurement (ROM), care procurement or performance agreements. In view of increasing requirements, it is especially important to safeguard the clinical relevance of such managerial information. Although the monitoring and evaluation of treatment outcomes is already considered essential to depression management, such procedures often confine themselves to organisational-level results based on the total costs or performance of service delivery, providing no indicators that could serve as input in an improvement cycle for individual care, as in stepped-care strategies. The strategic choice to be made here is to make individual treatment strategies the paramount focus in the continuous improvement process within healthcare organisations. Clinical relevance should always be the guiding principle and criterion, in clinical management as wel as in outcomes management. The outcomes measured should be of relevance to the patient in order to create value-based health care (Porter 2010; 2008; Porter & Teisberg 2006).

3.9 Interactions between the micro-, meso- and macrolevel: a depression care management process model

To aid in the development of depression management programmes at local or regional levels in accordance with the Chronic Care Model, a process model is introduced (see Figure 3.1). This model sets out a series of steps to be taken jointly by the parties involved to achieve quality and efficiency improvements in service delivery, such as in logistic care processes along the care continuum to ensure quality care from all providers involved, or in multidisciplinary care based on a coordinated strategy. Depression management can be performed within care teams that work to evaluate and improve clinical outcomes and to adapt care processes using outcomes management (Walburg 2003). Monitoring and evaluation in this process model focuses not only on improvement cycles for patient care processes, but also on adjusting individual treatment strategies and on integrating the acquired knowledge into professional standards of care. This keeps healthcare professionals motivated in a cycle of continuous improvement (Nash 2003).

The depression care management process model pictures feedback loops to operate between the patient level (microperspective), the care process level of service delivery (mesoperspective) and healthpolicy making from a shared vision on care at the macrolevel. Interactions between the micro-, meso- and macroperspective can benefit depression care. Examples of integrating mesolevel care improvements in the therapeutic process are: assessing and reviewing data concerning patient values and other critical information about the course and management of the condition; helping patients to set goals and solve problems for improved self-management; applying clinical and behavioural interventions that prevent complications and optimise disease control and patients well-being; providing evidence-based clinical care and self-management support; and ensuring continuous follow-up.

A successful improvement cycle from the micro-, meso- and macroperspective will have been achieved when depression care management does not focus on one or a few components, but when care processes are increasingly integrated, the application of evidence-based guidelines shows results, healthcare professionals become more proficient in clinical management, and the successful performance of healthcare organisations is reflected both in improved individual treatment results and in quality and efficiency improvements in service delivery.

In the process of quality and efficiency improvement, outcomes management delivers data that can help in determining the appropriate depression care management strategies. Conversely, a database containing monitoring and evaluation results can provide information to guide outcomes research. The research findings may be integrated into standards of care and decision support

tools for use in practice settings. To optimally implement and evaluate care improvement strategies, a knowledge base can be built to supply information to the various feedback loops between the microlevel, mesolevel and macrolevel. It could contain information on evidence-based interventions and the relative cost-effectiveness of various treatment alternatives, of available standards of care and decision support tools, as well as on successful depression care management strategies, relevant outcome and process indicators, and incentives to opt for and deliver quality of care. Also, the standards of care underlying care processes and individual care strategies can be improved, new improvement objectives can be set, and deficiencies in resources critical to the provision of services can be identified.

Macrolevel

Modify care vision?

Shared vision on care

Scope, aims, stakeholders, organisational structure of healthcare system, service delivery design, incentives in healthcare system, care management, care coordination, public control

Improvement objectives achieved?

Mesolevel

Standards of care

Evidence-based clinical practice guidelines and professional care standards, stepped-care decision support tools, care programmes, prevention programmes

Improvement objectives on quality and efficiency in service delivery

Implementation of self-management support, delivery system design, clinical information systems ans decision support

Monitoring and evaluation

Feedback data (outcomes, processes) on individual treatment strategies (clinical management) and care precesses (outcomes management), benchmarking data, performance indicators

Microlevel

Modify standards of care?

Individual patient goals

Individual treatment strategies
Stepped-care strategies

Individual patient goals achieved?

Table 1 *A depression care management process model with interactions between the micro-, meso- and macrolevel*

3.10 Conclusions

Depression care management is a coordinated approach to patient care with the aim of delivering care as efficient as possible with the best optimum of results while accounting for the nature, severity and progression of symptoms at all stages or states of depression. Depression care management that includes timely recognition and subsequent careful monitoring and evaluation of treatment outcomes can help to improve both the quality and efficiency of the healthcare delivery system and individual patient health gains. Measurable outcomes are central to both depression care management and stepped care.

The principles of stepped care fit well into depression care management, and a stepped-care approach can strengthen depression care management and add value to it. In addition to stepped care as a treatment strategy, that is steered by individual treatment outcomes, depression care management provides in a steering principle based on measurable outcomes at the mesolevel of service delivery. The routinely monitoring and evaluating of care processes by outcomes management is fundamental in chronic care management and can be united with clinical management as in a stepped-care approach. The paramount focus in monitoring and evaluating care should be on the relevance of it to the patient, in order to create value-based health care.

Proactive interactions between the micro-, meso- and macroperspective can benefit depression care. The depression care management process model describes how feedback loops can operate between the patient level (microperspective), care processes at the level of service delivery (mesoperspective) and healthcare policy making from a shared vision on care (macroperspective). Integrating evidence-based clinical practice guidelines and standards of care into care processes can contribute to achieving better treatment outcomes for individual patients (microperspective) and quality and efficiency improvement at the mesolevel of care.

Part II
Implementing
stepped care

Chapter 4

A stepped-care programme
for depression management: an
uncontrolled pre-post study in primary
and secondary care in the Netherlands

Summary

Introduction. Stepped-care strategies are potentially effective to organise integrated care but unknown is whether they function well in practice. This study evaluates the implementation of a stepped-care programme for depression in primary care and secondary care.

Theory and methods. We developed a stepped-care algorithm for diagnostics and treatment of depression, supported by a liaison-consultation function. In a 2½ year study with pre-post design in a pilot region, adherence to the protocol was assessed by interviewing 28 care professionals of 235 patients with mild, moderate, or severe major depression. Consultation and referral patterns between primary and secondary care were analysed.

Results. Adherence of general practitioners and consultant care professionals to the stepped-care protocol proved to be 96%. The percentage of patients referred for depression to secondary care decreased significantly from 26% to 21% (p=0.0180). In the post-period more patients received treatment in primary care and requests for consultation became more concordant with the stepped-care protocol.

Conclusions. Implementation of a stepped-care programme is feasible in a primary and secondary care setting and is associated with less referrals.

Discussion. Further research on all subsequent treatment steps in a standardised stepped care protocol is needed.

"Don't dwell on what has passed away or what is yet to be. ...
Ring the bells that still can ring. Forget your perfect offering."
Leonard Cohen, 1992, Anthem (There is a crack in everything)

4.1 Introduction

Depression is a common and frequently chronic mental disorder that can cause a high burden of disease and long periods of restrictions on psychological and social functioning (Murray & Lopez 1997; Ustün, Ayuso-Mateos, Chatterji, Mathers & Murray 2004). In one year, 736,000 people suffer from depression in the Netherlands and in the 18–65 age group costs of depression are estimated at € 2,100,000,000 a year, mainly due to the need for care and the absence from work (Smit 2006; Smit, Cuijpers, Oostenbrink, Batelaan, de Graaf & Beekman 2006). Depression varies in severity and prognosis (Kessing 2007; Judd, Akiskal, Maser, Zeller, Endicott, Coryell et al. 1998). Whereas fifty percent of the patients with a new major depressive episode recover within three months without intervention, patients who have not recovered six months after onset develop a high risk on chronic depression, estimated at 10–20% after two years. Additionally, whereas 60% of the patients with intervention are in remission after one year, in the year after remission of symptoms relapses occur in 30%, and in the year after full recovery recurrence occurs in 50–60% (Spijker 2002). This varying course of depression requires fine-tuning of the choice of consecutive treatment strategies.

Instead, although evidence-based clinical guidelines are available, depression is often under-treated or over-treated (Lecrubier 2007; ten Have, de Graaf, Vollebergh & Beekman 2004), thus impeding an adequate treatment match based on patient characteristics and nature and severity of symptoms. After the initial diagnosis and treatment in primary and secondary care, there is often no follow-up treatment or additional diagnostic procedure in case of non-remittance (van der Feltz-Cornelis, Wijkel, Verhaak, Collijn, Huyse & van Dyck 1996). This is a problem of high clinical and societal relevance.

The stepped-care model could provide a solution to this problem by aiming to initiate interventions at the right time and adequately: not earlier or more intensely

than necessary, not later or less intensely than needed (Bower & Gilbody 2005; Meeuwissen & Donker 2004; Haaga 2000; Davison 2000; Von Korff & Tiemens 2000). Stepped-care strategies prevent unnecessary treatment for most of the patients who will recover spontaneously or with minimal interventions. Symptoms are monitored carefully and patients who fail to respond or exhibit insufficient signs of recovery are easily detected and given appropriate treatment, 'stepping up' the treatment intensity.

In Dutch clinical practice, however, until the moment of starting this study, there are no sufficient practical tools to facilitate clinical decision making and structured collaboration among care professionals to support stepped-care treatment strategies tailored to individual needs. Moreover, although stepped-care strategies are potentially an effective way to organise integrated healthcare services (Bower & Gilbody 2005; Katon, Von Korff, Lin, Simon, Walker, Unützer et al. 1999; Katon, Russo, Von Korff, Lin, Simon, Bush et al. 2002; Sobell & Sobell 2000; Wilson, Vitousek & Loeb 2000), little is known about whether stepped-care programmes function well in practice.

In our study, for the first time, a stepped-care programme for depression in primary and secondary care was developed and tested in one region in the Netherlands. The programme consists of a stepped-care protocol in which a five-step algorithm for the diagnostics and treatment of depression is supported by a liaison-consultation function. The aim of the stepped-care protocol is to facilitate clinical decision making on the diagnostics and treatment of depression in primary and secondary care by improving diagnostic and treatment procedures for depressive disorder along the spectrum of severity.

4.2 Theory and methods

4.2.1 Theory and hypothesis

Our hypothesis was that the stepped-care programme would result in relatively fewer referrals to the Mental Health institution because appropriate treatment is delivered in primary care. The underlying assumption based on the stepped-care model is that working with the stepped-care algorithm supported by the liaison-consultation function improves coordination and cooperation between primary care and the Mental Health institution. In the application of the stepped-care algorithm, consultation and referral are regarded as vital links between the various treatment steps. The stepped-care protocol should integrate care processes across the care continuum and enable a clear division of tasks and responsibilities, leading to better quality of care at the patient level.

4.2.2 Design

This 2½ year study follows an uncontrolled pre-post design evaluating the implementation of the stepped-care protocol. The development and implementation of the stepped-care protocol followed the method of programme evaluation in which intermittent evaluation based on interview data served the continuous improvement of the stepped-care programme (Donker 1990).

Main outcomes on consultations and referrals are presented for the pre-period (January 2000 to March 2001) and post-period (April 2001 to June 2002). The reporting follows the TREND statement for nonrandomized evaluations (Des Jarlais, Lyles & Crepaz 2004).

4.2.3 Setting and subjects

The study was conducted from January 2000 to June 2002 in the pilot region Zeeuws-Vlaanderen, a catchment area of 380,226 inhabitants in the south of the Netherlands with 120 general practices and one Mental Health institution having 9,700 outpatient contacts a year and facilities for inpatient treatment of 290 patients. The pilot region is comparable to other regions in the Netherlands regarding the role of the general practitioner (GP) in depression care with respect to the understanding of one's tasks in diagnostics and treatment, and experienced bottlenecks in communication and cooperation with other care professionals, including consultation and referral (Visscher, Laurant, Schattenberg & Grol 2002).

Study subjects are patients in the 18–65 age group who sought treatment from a general practice or the Mental Health institution for a mild, moderate, or severe major depression as established in a psychiatric interview according to the DSM-IV criteria (American Psychiatric Association 2008). Patients with a manic episode, psychotic symptoms or suicidal ideation were excluded.

4.2.4 Intervention

The main component of the programme is the stepped-care protocol, i.e. a five-step algorithm for the diagnostics and treatment of depression supported by a liaison-consultation function. In the stepped-care algorithm, evidence-based treatment options and the sequence in which the interventions are considered are based on the state-of-the-art according to the Dutch Multidisciplinary Guideline for Depression (CBO/Trimbos Institute 2005) and the General Practitioners (NHG) Standard for Depressive Disorder (van Marwijk, Grundmeijer, Bijl, Gelderen, de Haan, van Weel-Baumgarten et al. 2003) (see Box 1 and Figure 1). The treatment options were standardised as modules in the stepped-care programme (Meeuwissen & van Weeghel 2003). For each treatment option directions for monitoring and evaluation as key elements in stepped care, were described.

In the liaison-consultation function the Mental Health institution psychiatrist or psychotherapist advises the general practitioner (GP) on request for any reason, for example on diagnosis, treatment and referral according to the stepped-care algorithm. The stepped-care protocol describes how consultants in the liaison-consultation function can be reached, how patients should be referred within the primary care system and from primary care to secondary care, how the referring GP should be informed about the treatment progress, and how the care process should be coordinated between the GP and other care professionals according to the five steps in the algorithm with explicit decision points for evaluating diagnosis and treatment.

4.2.5   Development and implementation

To develop and implement the stepped-care protocol a regional multidisciplinary task force was established with 4 GPs and 2 social workers, 1 psychologist/psychotherapist and 1 pharmacist in primary care, 4 psychologists/psychotherapists and 2 psychiatrists from the Mental Health institution, as well as researchers from the Trimbos Institute. The work group met at 10 bimonthly sessions to discuss the applicability, practical usefulness and clinical value of the stepped-care protocol, in the first stage resulting in criteria for the programme evaluation (see Process and outcome measures).

The stepped-care protocol was introduced in the region at regular meetings for continuing education of care professionals. An expert committee supervised the process at three-monthly meetings where the stepped-care protocol was presented for feedback. Based on intermittent findings in the interview data the stepped-care protocol was adjusted.

To preclude a Hawthorne effect, the task force that developed the stepped-care protocol was a different group of care professionals (n=14) than the group that put the protocol into effect (n=28). The task force instructed a group of colleagues to use the stepped-care protocol in daily practice. Only 5 care professionals participated in both groups. All 28 care professionals were interviewed for evaluation purposes (see Data collection and Analysis).

4.2.6   Data collection

Source I: description of caseloads and process measures. The participating care professionals selected from the patients in the 18–65 age group in their caseload every patient whom they had treated for a mild, moderate, or severe major depressive disorder in the past six months. A total of 235 patients were eligible for the evaluation, which is 3–5 per care professional. Data were collected in a baseline interview with the care professionals at the start of the project (T0) and

two follow-up interviews after 6 months (T1) and after 12 months (T2), all with the same interviewer. These semi-structured interviews provided data on patient characteristics in their caseloads and process measures on treatment policy for these patients, as well as data for the intermittent programme evaluation (Table 1).

Source II: consultations and referrals. Institutional data on the 164 consecutive patients who were subjects of consultations by care professionals of the Mental Health institution, and on the 344 consecutive referrals for depressive disorder, were recorded by the research coordinator during the study period, providing data on the main outcomes (Table 1). For the timeline in data collection see Figure 2.

4.2.7 Process and outcome measures

Process measure was adherence of GPs and care professionals at the Mental Health institution to the stepped-care protocol. This was assessed by self report in the semi-structured interviews providing data for Source I on the question whether the care professional treats patients in accordance to the stepped-care protocol. Also, the clinical value of its application as perceived by care professionals was asked for. Main outcomes measured are number of consultations and referrals as well as consultation and referral characteristics such as reasons for consultation and referral. Furthermore, the Mental Health institution and neighbouring Mental Health institutions were asked if they used the protocol after completion of the study.

4.2.8 Analysis

Descriptive statistics on sociodemographic variables and clinical characteristics included mean and frequency analyses using t-tests and X^2-tests. Mann–Whitney and Fisher-Exact tests were used for the pre-period and post-period outcome comparisons.

4.3 Results

4.3.1 Patient characteristics

No significant differences in the caseloads of interviewed care professionals at the several measurement points were found. Patient characteristics and established diagnostic categories for consultation and referral are summarised in Table 2.

The figures on the consultation of in total 164 depressed patients constitute 39% of all the consultation contacts in the study period. No significant differences in demographic characteristics were found between the pre-period and post-period.

Also, patients in the pre-period and post-period did not differ significantly in the number of complaints or the preceding history of the symptoms.

The institutional referral figures on the 344 depressed patients pertain to 24% of all the patients referred to the Mental Health institution in the study period in the region. No significant differences in patient characteristics were found between the pre-period and post-period. A significant difference is found between the periods on axis IV, with more psychosocial or social problems co-occurring in the pre-period

START → Depression evaluation

Step 1 *Psychoeducation or Selfhelpcourse*

Depression evaluation → Complete remission → Relapse prevention

Partial remission

Step 2 *Practical interventions, Counseling, Running therapy or Brief therapy*

Depression evaluation → Complete remission → Relapse prevention

Partial remission

Step 3 *Cognitive (behavioral) therapy, Interpersonal therapy or Pharmacotherapy*

Depression evaluation → Complete remission → Relapse prevention or individual reintegration

Partial remission

Figure 1   Stepped-care algorithm for diagnostics and treatment of depression

The five-step algorithm cites the sequence in which minimal interventions, systematic psychotherapy, biological therapy and non-specific interventions for support, care and reintegration are considered when initiating and adjusting individual treatment policy (Figure 1).

Treatment choices are jointly made by the care professional and patient at structured evaluation moments based on nature and severity of symptoms, earlier treatment results, treatment progress and patient preferences until the treatment goals are reached.

Step 1, the least invasive intervention, consists of psycho-education or a self-help course, e.g. in the form of bibliotherapy (Scoging, Hanson, Welsh 2003). In Step 2, practical interventions, counseling, brief problem-solving therapy or running therapy are initiated. Step 3 consists of cognitive therapy, cognitive behavioural therapy, interpersonal therapy, pharmacotherapy or St. John's Worth. In Step 4 either of the forms of psychotherapy or pharmacotherapy is added to Step 3. In seasonal depression light therapy is offered instead. If Step 5 is needed to support the interventions in a therapeutical setting or after pharmacotherapy, admission of electro convulsion therapy is indicated. Each step is succeeded by relapse prevention, aftercare or individual reintegration. Interventions are standardised to facilitate the appropriate treatment choices and referrals, anticipating the effectiveness of treatment alternatives and making a comparison possible of the treatment evaluation (see Figure 1). The five-step algorithm cites the sequence in which minimal interventions, systematic psychotherapy, biological therapy and non-specific interventions for support, care and reintegration are considered when initiating and adjusting individual treatment policy (Figure 1). Treatment choices are jointly made by the care professional and patient at structured evaluation moments based on nature and severity of symptoms, earlier treatment results, treatment progress and patient preferences until the treatment goals are reached.

Box 1   Interventions in the stepped-care algorithm for diagnostics and treatment of depression

(62% vs. 76%; p=0.0006). These patients appear to have been less frequently referred to the Mental Health institution in the post-period, in accordance with the stepped-care protocol.

4.3.2 Number and reasons for consultation and referral

Pre-period and post-period observations on the numbers of patients and reasons for consultation and referral are summarised in Table 3.

In the post-period, the reasons for consultation increased significantly from mean 1.56 to mean 1.81 (p=0.0037). The frequency of consultations on the communication or interaction of care professionals with the patient, instead of for example medication being prescribed, increased significantly from 9% to 33% (p=0.0000). In the post-period, the reasons for referrals are more frequently specified than in the pre-period.

Whereas the total number of referrals remains about the same, the comparative number of referrals for depression from primary care to the Mental Health institution significantly decreases from 26% of all referrals in the pre-period to 21% of all referrals in the post-period (p=0.0180). The percentage of depressed patients who come in for consultation does not differ significantly between the pre-period and post-period. These findings confirm our study hypothesis.

4.3.3 Adherence

The interviewed care professionals reported significant improvement from 88% adherence to evidence-based guidelines on depression at baseline to 96% adherence to the stepped-care protocol at follow-up (p=0.0089). In the small non-adherent group, reasons for non-adherence to the stepped-care protocol include: fear of following the stepped-care protocol rigidly or inflexibly and criticism of protocols in general, an excessive workload that does not leave time for change

Data source	Assessment	Number of patients
Source I	Semi-structured interviews (n=28) with care professionals at T0 (n=19; 10 GPs and 9 care professionals from the Mental Health institution), T1 (n=24; 8 GPs, 8 care professionals from the Mental Health institution, 6 social workers, and 2 primary care psychologists) and T2 (n=20; 8 GPs and 8 care professionals from the Mental Health institution, 3 social workers, and 1 primary care psychologist)	T0: n=81 patients with depression from caseloads in previous 6 months; T1: n=87 patients with depression from caseloads since T0; T0: n=67 patients with depression from case-loads since T1

Constructs (process measures)	Unit of analysis
– Description of caseloads	Patient level
– Adherence of care professionals to stepped care protocol	Care professional level
– Clinical implications according to care professionals at T2	Care professional level
Source II	Institutional data on consultations in pre-period and post-period	n=164 Pre-period: n=81 Post-period: n=83
Constructs (outcome measures)	Unit of analysis
– Patient and consultation charactristics	Patient level
– Reason for consultation	Care professional level
– Number of consultations	Institutional level
Source III	Institutional data on referrals in pre-period and post-period	n=344 Pre-period: n=174 Post-period: n=170
Constructs (outcome measures)	Unit of analysis
– Patient and referral characteristics	Patient level
– Reason for referral	Care professional level
– Number of referrals	Institutional level

Table 1 Constructs, data sources, assessments, number of patients and unit of analysis

and the expectation of extra consultation time involved, the excessive number of disciplines involved and not knowing other care professionals well enough, unfamiliarity with the protocol, dealing with old routines by colleagues, or no need for a protocol assuming that one implicitly follows the protocol.

4.3.4 Clinical implications according to care professionals

The perceived clinical implications in the post-period are summarised in Table 4. According to the care professionals interviewed at T2, the stepped-care programme provides a structured, standard approach that highlights the clinical decisions to be made during the care process. The way the care process is organised becomes more transparent. Various disciplines share a frame of reference with the stepped-care protocol, and have a shared view on an integrated care process in which each care professional's tasks and responsibilities are defined.

Baseline T0 At start of study	Follow-up T1 After 6 months	Follow-up T2 After 12 months	Source I Description of caseload and proces measures (n=235)
Patients with depression from caseload in previous 6 months (n=81)	Patients with depression from caseload since T0 (n=87)	Patients with depression from caseload since T1 (n=67)	

Pre-period January 2000-March 2001	Post-period April 2001-June 2002	Source II
Consultations (n=81)	Consultations (n=83)	Consultations (n=164)
Referrals (n=174)	Referrals (n=170)	Referrals (n=344)

Jan-00 **T0** Jul-00 **T1** Apr-01 Jul-01 **T2** Jun-02
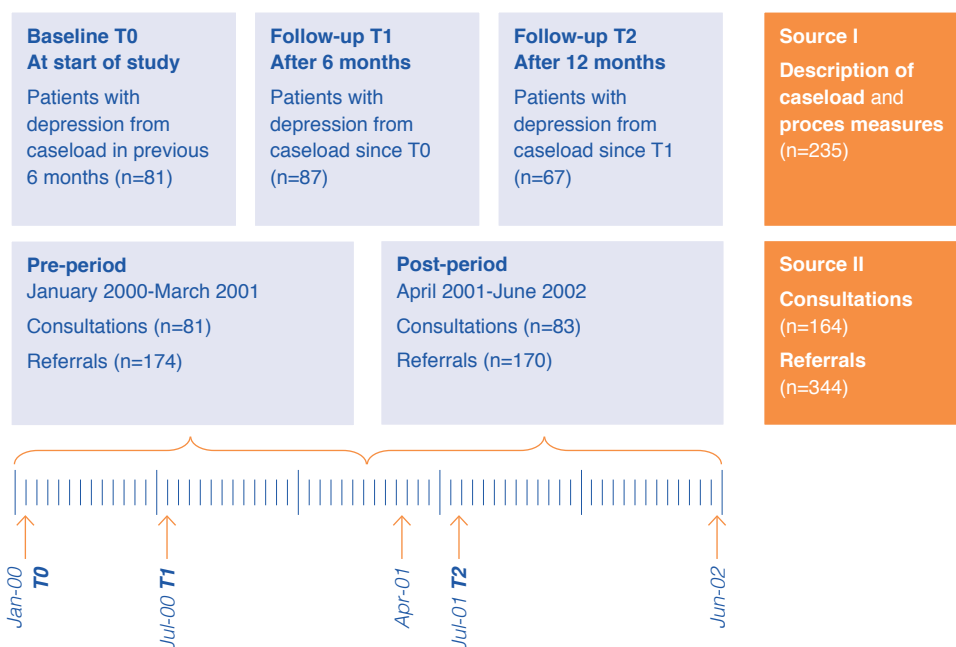
Figure 2 *Timeline in data collection in Source I and Source II*

4.3.5 Implementation at end of the study

The stepped-care protocol is still being used in the pilot region. To the general satisfaction of the GPs, the liaison-consultation function has been expanded to include a psychologist from the secondary mental healthcare institution operating structurally in 60% of the general practices. Two Mental Health institutions in neighbouring regions that were asked if they used the protocol did so to their satisfaction: a neighbouring region in the Netherlands, Brabant, has adapted the protocol, as has a region in Belgium with 500,000 residents with good results (Coster, Audenhove, Goetinck & Ameele 2004).

	Consultations n=164	Referrals n=344
Age (mean years)	47	39
Female	102 (62%)	211 (61%)
Living with partner and child(ren)	52 (31%)	
Mental disorder		
Co-morbid problems on axis I	78 (48%)	82 (24%)
Anxiety disorder	35 (21%)	30 (9%)
Substance abuse disorder	7 (4%)	25 (7%)
Relationship problems	25 (15%)	

Table 2 *Patient characteristics and diagnosis*

4.4 Discussion

4.4.1 General conclusions

This study shows that adherence to the stepped-care protocol can be reached. The comparative number of referrals from primary care to the Mental Health institution decreased significantly while the percentage of patients for whom consultation was requested remains the same. In the post-period, more patients received treatment in the primary care setting. The number of reasons for consultation increased per patient and consultation questions pertaining to the preferable care professional's way of communicating or interacting with the patient rise in the post-period. According to the interviewed care professionals, the stepped-care protocol plays an important role in supporting diagnostics, treatment choices and intermittent evaluations at critical decision points in the stepped-care treatment strategies. These findings confirm our study hypothesis. They are consistent with randomised clinical trials showing that collaborative care or support interventions improve patient outcomes (Katon, Von Korff, Lin, Simon, Walker, Unützer et al. 1999; Katon, Russo, Von Korff, Lin, Simon, Bush et al. 2002; Katon, Von Korff, Lin, Walker, Simon, Bush et al. 1995; Katon, Robinson, Von Korff, Lin, Busch, Ludman et al. 1996; Unützer, Katon, Callahan, Williams, Hunkeler, Harpole et al. 2002).

4.4.2 Limitations of the study

One limitation of the study might be that coordination and cooperation would be improved as a specific effect by better collaboration between care professionals, regardless of the content of the care process, but this was not borne out by the results: over 90% of the care professionals adhered to the stepped-care protocol. However, adherence to the stepped-care protocol was assessed by self report in semi-structured interviews, which possibly resulted in an overestimation of adherence. Also, the pilot region might be differing from other regions in self reported adherence to evidence-based guidelines at baseline, although we have no reason to assume that adherence to guidelines or protocols is varying between regions.

In this study we had no data describing the flow per patient through the programme, only clustered institutional data indicating that patients are sufficiently dealt with at lower steps. More specific results should be established in a randomised clinical trial exploring the effectiveness all subsequent steps as well as of the entire protocol.

4.4.3 Research implications

In this study, the liaison-consultation function facilitates implementation of the

stepped-care algorithm. This is in line with studies describing several types of multidisciplinary consultation about diagnosis, treatment or referral, such as the nurse practitioner or the psychiatrist (Katon, Von Korff, Lin, Walker, Simon, Bush et al. 1995; Katon, Robinson, Von Korff, Lin, Busch, Ludman et al. 1996; Unützer, Katon, Callahan, Williams, Hunkeler, Harpole et al. 2002; van der Feltz-Cornelis, Oppen, Adèr, van Dyck 2006; Kates, Craven, Bishop, Clinton, Kraftcheck, LeClair et al. 1997; Badamgarav, Weingarten, Henning, Knight, Hasselblad, Gano et al. 2003). In this study, we did not distinguish consultation as a separate step as in other studies (Von Korff & Tiemens 2000), assuming it can be supporting all interventions in the stepped-care algorithm (Klinkman 2003; Trivedi, Rush, Crismon, Kashner, Toprac, Carmody et al. 2004). As regards the actual sequence of evidence-based interventions, deviating from other studies (Goldberg 2006; Fortney, Pyne, Edlund, Robinson, Mittal & Henderson 2006), we position pharmacotherapy either in the same step, or after brief psychotherapy such as cognitive or cognitive behavioural therapy or interpersonal therapy. This is in line with the Dutch evidence-based Multidisciplinary Guideline for Depression.

Consultations	Pre-period n = 81	Post-period n = 83	Statistic
Percentage of subjects for consultation for depression	41%	38%	n.s.
Consultation asked by			
General practitioner	65 (80%)	48 (58%)	n.s.
Other	16 (20%)	48 (42%)	n.s.
Consultation given by			
Psychiatrist	69 (85%)	52 (63%)	n.s.
Psychologist/psychotherapist	7 (9%)	7 (8%)	n.s.
Consultation by telephone	58 (72%)	61 (73%)	n.s.
Mean number of reasons for consultation	n = 81 1.56 ± 0.69	n = 83 1.81 ± 0.83	t-test t = − 2.105; df = 162; sig = 0.037
Topic of consultation advice	n = 81	n = 67	
Medication	50 (62%)	39 (58%)	n.s.
Advice on referral	21 (26%)	25 (37%)	n.s.
Other treatment advice	29 (36%)	17 (25%)	n.s.
Advice on communication and interaction with the patient	7 (9%)	22 (33%)	x^2 = 13.623; df = 1; sig = 0.000
Advice on diagnostics	18 (22%)	11 (16%)	n.s.
Advice on somatic diagnostics	2 (2%)	0 (0%)	n.s.
Other topic	0 (0%)	3 (4%)	x^2 = 3.702;df = 1; sig = 0.054

Referrals	Pre-period n = 174	Post-period n = 170	Statistic
Percentage of referrals for depression	26%	21%	Fisher Exact sig; p = 0.0180
Referral	n = 171	n = 168	
By General practitioner	150 (88%)	154 (92%)	n.s.
By other	21 (12%)	14 (8%)	n.s.
Reason for referral (if given)	n = 99	n = 138	
Severity of symptoms	48 (49%)	71 (51%)	n.s.
No recovery	21 (21%)	28 (20%)	n.s.
Indication for psychotherapy	6 (6%)	16 (12%)	n.s.
Direct intervention needed	0 (0%)	5 (4%)	n.s.
Unclear diagnosis/treatment	12 (12%)	16 (12%)	n.s.
Other reason	12 (12%)	2 (1%)	$x2 = 16.741$; df = 5; sig = 0.005

Table 3   Number and reasons for consultations and referrals

In Dutch secondary health care, it is common for patients to follow an extensive procedure matching treatment choice to patient characteristics prior to the start of treatment based on specific patient needs and characteristics. In a pragmatic randomised trial on the treatment of anxiety and depression at secondary mental health centres, this extended procedure proved to be no more effective than either brief therapy with restrained sessions or cognitive therapy as a first step, demonstrating that brief therapy can be a more efficient first step (van Straten, Tiemens, Hakkaart, Nolen & Donker 2006). These findings support the intervention sequencing in steps 2 and 3, as in the stepped-care algorithm described in this study.

This is the first and only completed study in the Netherlands to systematically evaluate the feasibility of a stepped-care algorithm with standardised treatment steps covering the whole continuum from prevention, diagnostics, cure and care to reintegration, based on evidence-based guidelines. Given the positive outcome of this study, an explorative study that gives directions for clinical parameters for 'stepping up' in the stepped-care algorithm will be interesting. A cost-effectiveness study should be performed to establish the efficiency of following all treatment steps in a standardised stepped-care protocol.

4.4.4 Further implementation

As is shown by the implementation follow-up the stepped-care protocol is adopted and can be generalised to other regions and the barriers perceived before implementation can be accounted for. In a 'breakthrough series approach', parts of the stepped-care protocol have been adapted for implementation nationwide

Appropriate treatment
– Earlier recognition of depression

– Timely referral if necessary

– More patients receive adequate treatment

– Less under-treatment, less over-treatment

Collaborative care and streamlining the care process
– Support by intercollegial consultation on diagnostics and treatment choice

– Improved consultative structure and feedback with referrer on treatment results

– Improved gearing of follow-up activities

Other quality of care aspects
– Support on clinical decision making

– Improved monitoring of the course of depression and evaluation of treatment results

– Shorter waiting times and accessible care for the patient

– Explicit and efficient process, increased reference points

Table 4   Clinical implications of stepped-care protocol perceived by care professionals

to improve the quality of care (Franx, van Wetten, van Duin & Henkelman 2006; chapter 5). This demonstrates that the five step algorithm together with a supportive liaison-consultation function between primary and secondary care is a feasible and generalisable method to implement evidence-based diagnostics and treatment for patients with a depressive disorder in the Netherlands.

4.5 Conclusion

Our study can contribute to clinical practice in three ways: by structuring treatment steps across the care continuum, by supplying practical tools that enable care professionals to choose evidence-based treatment strategies regarding the severity and course of depression, and by demonstrating the feasibility of the stepped-care protocol in daily practice.

Chapter 5

Quality improvement in depression care
in the Netherlands: the Depression
Breakthrough Collaborative.
A quality improvement report

Summary

Background. Improving the health care for patients with depression is a priority health policy across the world. Roughly, two major problems can be identified in daily practice: (1) the content of care is often not completely consistent with recommendations in guidelines and (2) the organisation of care is not always integrated and delivered by multidisciplinary teams.

Aim. To describe the content and preliminary results of a quality improvement project in primary care, aiming at improving the uptake of clinical depression guidelines in daily practice as well as the collaboration between different mental healthcare professionals.

Method. A Depression Breakthrough Collaborative was initiated from December 2006 until March 2008. The activities included the development and implementation of a stepped-care depression model, a care pathway with two levels of treatment intensity: a first step treatment level for patients with non-severe depression (brief or mild depression symptoms) and a second step level for patients with severe depression. Twelve months data were measured by the teams in terms of one outcome and several process indicators. Qualitative data were gathered by the national project team with a semi-structured questionnaire amongst the local team coordinators.

Results. Thirteen multidisciplinary teams participated in the project. In total 101 care professionals were involved, and 536 patients were diagnosed. Overall 356 patients (66%) were considered non-severely depressed and 180 (34%) patients showed severe symptoms. The mean percentage of non-severe patients treated according to the stepped-care model was 78%, and 57% for the severely depressed patient group. The proportion of non-severely depressed patients receiving a first step treatment according to the stepped-care model, improved during the project. This was not the case for the severely depressed patients. The teams were able to monitor depression symptoms to a reasonable extent during a period of 6 months. Within 3 months, 28% of monitored patients had recovered, meaning a Beck Depression Inventory (BDI) score of 10 and lower, and another 27% recovered between 3 and 6 months.

Conclusions and discussion. A stepped-care approach seems acceptable and feasible in primary care, introducing different levels of care for different patient groups. Future implementation projects should pay special attention to the quality of care for severely depressed patients. Although the Depression Breakthrough Collaborative introduced new treatment concepts in primary and specialty care, the change capacity of the method remains unclear. Thorough data gathering is needed to judge the real value of these intensive improvement projects.

5.1 Introduction

Policies aiming to create an evidence-based mental healthcare system, offering appropriate care to patients and delivering better outcomes, have not been successful until now. According to the European Study of the Epidemiology of Mental Disorders (ESEMED) conducted in six western countries including the Netherlands, of all patients treated for an anxiety disorder or a depressive disorder, 57% were treated appropriately in secondary care and only 23% received the right treatment in primary care (Fernandez, Haro, Martinez-Alonso, Demyttenaere, Brugha, Autonell et al. 2007).

Major depressive disorder (MDD) (American Psychiatric Association 1994) is a prevalent condition worldwide: 12 months-prevalence of MDD ranges from 4 to 10% and a lifetime prevalence of 15 to 17% (Regier, Narrow, Rae, Manderscheid, Locke & Goodwin 1993; Kessler, McGonagle, Zhao, Nelson, Hughes, Eshleman et al. 1994; Offord, Boyle, Campbell, Goering, Lin, Wong et al. 1996; Bijl, Ravelli & van Zessen 1998). In the Netherlands Mental Health Survey and Incidence Study (NEMESIS) (Bijl, Ravelli & van Zessen 1998; Bijl, van Zessen, Ravelli, de Rijk & Langendoen 1998) a median duration of new depressive episode of 3 months was found, 63% of those with a new episode had recovered within 6 months and 76% in 12 months. Almost 20% of those affected had not recovered in 24 months (Spijker, de Graaf, Bijl, Beekman, Ormel & Nolen 2002). Primary care is the key supplier of care to patients, because of the high prevalence of patients with depression or depressive feelings in general practice of around 21% (van' t Land, Grolleman, Mutsaers & Smits 2008). Despite policy incentives to strengthen the capacities of primary care, general practitioners still refer more patients to a more expensive form of care in specialty care than to psychologists and social workers in primary care (van' t Land, Grolleman, Mutsaers & Smits 2008; van Balkom 2005).

Two depression guidelines are actually available to Dutch practitioners, recommending effective interventions for different subgroups of patients. The

Multidisciplinary Guideline for Depressive Disorder, adopted in 2005 by a range of professional organisations in specialised mental health, and the depression standard, adopted by general practitioners in 2003 (Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ 2005; van Marwijk, Grundmeijer, Bijl, van Gelderen, de Haan, van Weel-Baumgarten et al. 2003). Following depression guidelines can be of value to professionals as applying the effective interventions recommended in guidelines can lead to better outcomes for patients and to lower costs to society (Andrews, Issakidis, Sanderson, Corry, Lapsley 2004; Chisholm, Sanderson, Ayuso-Mateos & Saxena 2004; Adli, Bauer & Rush 2006; Bauer 2002; Hodiamont 2001; Grol, Wensing & Eccles 2005). Unfortunately, the uptake of the depression guideline recommendations in Dutch daily practice has been slow. A study looking into evidence-based depression care in 1999, concluded that previous depression guideline editions were considered to be too globally formulated, giving insufficient tools to practitioners for decision support in daily practice (Ormel, Bartel & Nolen 2003; Tiemeier, de Vries, Kahan, Klazinga, Grol et al. 2002; Spies, Mokkink, de Vries Robbé & Grol 2004; Cepoiu, McCusker, Cole, Sewitch, Belzile & Ciampi 2008). Other implementation barriers can be related to characteristics of the professionals and the patients, and environmental factors such as a lack of support from peers or superiors, insufficient staff or time, and poor collaboration between professionals (Grol, Wensing & Eccles 2005; Francke, Smit, de Veer & Mistiaen 2008).

The effective treatments proposed in the depression guidelines published in the Netherlands in the spring of 2009, range from less intensive interventions like psychoeducation or self help intervention (individual or group courses), problem solving treatment (PST), and physical exercise (running therapy), to more intensive treatments such as cognitive behavioural therapy, pharmacotherapy and electroconvulsion therapy. Considering the heterogeneous course of MDD, the selection of the appropriate intervention and the organisation of depression care needs to be built on careful timing and paced appropriately. Goals of treatment should be to avoid over-treatment in those with a favourable prognosis and to prevent the development of chronic symptoms in those depressed individuals with an unfavourable prognosis (under-treatment).

Over-treatment of minor and mild-major depressions is seen in general practice where antidepressant drugs are prescribed to 68% of the patients, regardless of the severity of depression (Spies, Mokkink, de Vries Robbé & Grol 2004; Braspenning, Schellevis & Grol 2004). Also, antidepressants in many cases are prescribed over too long a period of time (DGV 2008). This is contrary to guideline recommendations and studies that advise less intensive treatments in mild cases because there is no additional effectiveness of antidepressant treatment over counseling alone (Spies, Mokkink, de Vries Robbé & Grol 2004; Spijker, Bijl, de Graaf & Nolen 2001; van Rijswijk 2005; Hermens 2005). Less intensive treatment alternatives are insufficiently known and not made available or used by primary

care professionals, despite the fact that they have been proven to be effective in randomised controlled trials in The Netherlands (Smit 2007).

Under-treatment of patients with more severe symptoms, is caused by provider barriers including concerns about patient stigma, time pressures, inadequate knowledge about diagnostic criteria and treatment options, and a lack of psycho-social orientation. Also, poor recognition of depression by general practitioners has been reported; in one study 33% of cases were not diagnosed as depression or any other psychological disease. Moreover, patient-provider communication concerning pharmacotherapy can be improved (Volkers, de Jong, de Bakker & van Dijk 2005). Patient related causes include somatic presentation of depression by patients and resistance to a diagnosis of depression. Once pharmacotherapy is started, compliance is low. Up to 37% of patients stop taking medication too soon, after one or two prescriptions, whereas 15–45% stop psychotherapy treatment too early (Ormel, Bartel & Nolen 2003; DGV 2008). System barriers include productivity pressures, limitations of mental health coverage, restrictions of specialists and treatments, the lack of a systematic method for detecting and managing depressed patients and inadequate continuity of care (Cepoiu, McCusker, Cole, Sewitch, Belzile & Ciampi 2008).

One of the methods to overcome barriers and improve the content and organisation of care is the Breakthrough Series Collaborative, because of its ability to enhance the rate of diffusion of existing science into clinical practice, by using multi-institutional or multisite work groups (Kilo 1999; Pearson, Wu, Schaefer, Bonomi, Shortell, Mendel et al. 2005; Greenhalgh, Robert, Macfarlane, Bate & Kyriakidou 2004; ØVretveit, Bate, Cleary, Cretin, Gustafson, McInnes et al. 2002; Schouten, Hulscher, van Everdingen, Huijsman & Grol 2008). In this study, we present the content and results of a part of a large Breakthrough Collaborative project targeting better outcomes for patients suffering from depression. The information presented is directed at the improvements for adult patients in primary care. The collaborative was initiated by the Netherlands Institute of Mental Health and Addiction, operated from December 2006 to April 2008, and was funded by a national health insurers fund, as part of the depression initiative programme (van der Feltz-Cornelis, Henkelman & Walburg 2006).

In the remainder of this chapter, we describe the problems in depression care targeted by the participants in this project, the improvement principles and goals, the improvement method, the methods used to collect and analyse the data, and the impact on key outcome and process indicators. In the discussion, the results are interpreted and compared to similar work, giving suggestions for future quality improvement projects.

5.2 Methods

5.2.1 Improvement principles and goals

A national expert team of depression opinion leaders and project coordinators was set in place. They developed a project plan, containing improvement principles, goals and suggestions for improvement ideas. The overall improvement principle was the implementation of a stepped-care approach. In a stepped-care approach evidence-based treatment options are ranked by their degree of intensity, looking at the impact on the patients life, the length of treatment, the setting (general practice or specialty care) and the costs, as well as combinations of these criteria (Meeuwissen & van Weeghel 2003; Meeuwissen, van der Feltz-Cornelis, van Marwijk, Rijnders & Donker 2008; Meeuwissen & Donker 2004). Patients start to step in at the appropriate intensity level, which matches their (severity) profile. Stepped-care models have the potential to improve efficiency and effectiveness of depression care (Katon, Von Korff, Lin, Simon, Walker, Unützer et al. 1999; Haaga 2000; Bower & Gilbody 2005). Also, the implementation of a stepped-care model can lead to better collaboration and integration, involving all partners across primary and secondary care, and making them aware of their individual contributions to the shared approach (Meeuwissen, van der Feltz-Cornelis, van Marwijk, Rijnders & Donker 2008; Meeuwissen & Donker 2004; Bower & Gilbody 2005; Von Korff & Tiemens 2000).

A pragmatic stepped-care model was developed (Figure 1), consisting of a depression care pathway with two levels of treatment intensity: a first step treatment level for patients with mild depressive symptoms and a second step treatment level for patients with severe depressive symptoms. The stepped-care model was based on previous projects in Dutch mental health care and on the (inter)national literature (Meeuwissen & van Weeghel 2003; Meeuwissen, van der Feltz-Cornelis, van Marwijk, Rijnders & Donker 2008).

Professionals applying all the elements of the stepped-care depression model, needed to implement the following changes in their practices:

1 *Stepped diagnostics.*

Depressive episodes were diagnosed as usual, with general practitioners using the ICPC coding system for new cases. Differentiation between patients with non-severe depressive symptoms (patient group 1 in Figure 1) and patients with severe symptoms (patient group 2 in Figure 1) had to be made, based on a set of severity criteria (see box in left lower bottom of Figure 1). For severely depressed patients a DSM-IV assessment was indicated.

2   *Stepped treatment.*

Implementation of a treatment pathway with two treatment levels: a first step level consisting of interventions for first, mild depressive episodes with a duration up to 3 months (treatment pathway level 1 in Figure 1) and a second step level mainly consisting of antidepressant medication and effective psychotherapeutic interventions (treatment pathway level 2 in Figure 1).

3   *Monitoring and evaluation of the treatment plan.*

The course of symptoms and treatment progress were to be monitored in both pathways using the Beck Depression Inventory (BDI).

Derived from this stepped-care model a set of SMART-goals was formulated; goals that are specific, measurable, attractive, realistic and timely (Table 1). These two instruments, the Stepped-care Depression Model and the set of SMART-goals, provided the improvement teams with guidance for their improvement work. The teams made a selection of goals, developed additional local goals if they wished and implemented changes.

5.2.2   Breakthrough method

The Breakthrough method, developed by Berwick and colleagues at the Institute for Healthcare Improvement in Boston (http://www.ihi.org), was used as the model for change during the collaborative (Berwick 1998). This method was chosen for various reasons. Firstly, Breakthrough Collaboratives are attractive projects, creating learning opportunities for professionals, offering them knowledge, a model for change and permitting them to spend time on testing changes and experimenting with new behaviour. Breakthrough Collaboratives can be especially useful for microsystem improvements, within small units of care delivery (Nelson, Batalden & Godfrey 2007). Secondly, these projects have become very popular over the last few years within the Dutch Ministry of Health, which has funded many in different healthcare settings. This positive reputation is only partly based on research literature. A systematic review of quality improvement collaboratives showed that the underlying evidence is positive but limited, with modest effects on outcomes at best (Schouten, Hulscher, van Everdingen, Huijsman & Grol 2008). In mental health care, the Breakthrough method had rarely been applied and evaluated.

Breakthrough Collaboratives can be considered as a multifaceted implementation strategy. Central characteristics of all Breakthrough Collaboratives are: the use of guidelines, local multidisciplinary improvement teams consisting of professionals and a local team coordinator, a national expert team consisting of depression opinion leaders and national project coordinators, data collection and continuous feedback loops (ØVretveit, Bate, Cleary, Cretin, Gustafson, McInnes et al. 2002; van Splunteren, van Everdingen, Janssen, Minkman, Rouppe van de Voort,

Schouten et al. 2003). In the Depression Breakthrough Collaborative a specific mix of these improvement strategies was offered to the participating teams (Table 2). A central feature of the Breakthrough Collaboratives is continuous feedback loops according to the Nolan model (Figure 2). The model consists of two elements: three questions to focus the improvement work and a PLAN-DO-STUDY-ACT (PDSA) cycle. This model, originally developed by Langley and popularised by Nolan, provides an overarching framework for testing change ideas that are expected to make progressively more complex changes along an improvement ramp. Instead of focusing on changing the behaviour of individual providers, the focus is on gradually changing organisations into high performing (micro)systems

Treatment pathway level 1

I First step interventions during 6-12 wks:

Watchful waiting
Psycho-education
Selfhelp, group or individual
Counseling
Brief psychotherapy, 8 sessions
Physical exercise
Other

II Monitoring

1 BDI per 6 weeks

Patient group 1:
Symptoms not severe*

General practitioner

- Check symptoms and registrate ICPC codes P03/P76
- Check symptom severity
- Appoint to patient group

Treatment pathway level 2

DSM-IV diagnosis

Start treatment within 1 month

Psycho-education

Depression treatment

Antipressants
Pyschotherapy; GT, CGT, IPT
Other

Drop-out reduction

Monitoring

1 BDI per 6 weeks

Patient group 2:
Symptoms severe*

* Severe symptoms in this model are:

- Symptoms duration longer than 6 months or

- Insufficient response to level 1 treatment after 3 months or

- Suicidal ideation, psychotic features, high level of social disfunctioning, inability to normal role taking (work, self care, taking care of others).

Figure 1   Stepped-care depression model

1	Within 6 months of treatment, 80% of all new patients have a score of 10 or lower on the Beck Depression Inventory (BDI). *Obligatory goal*
2	80% of systematic follow-up visits is according to planning, meaning 1 visit every 6 weeks until the scores on the BDI is 10 or lower. *Obligatory goal*
3	<10% of patients with non-severe symptoms receive antidepressants or psychotherapy as a first step treatment
4	All patients with severe depressive symptoms start treatment within 1 month after diagnosis
5	<20% of all patients with severe symptoms, treated with antidepressants, have dropped out of treatment within the first 3 months

Table 1   **The SMART goals of the Depression Breakthrough Collaborative**

of care (Nelson, Batalden & Godfrey 2007; van Splunteren, van Everdingen, Janssen, Minkman, Rouppe van de Voort, Schouten et al. 2003; Langley, Nolan, Norman, Provost & Nolan 1996).

5.2.3   Data collection and analysis

Quantitative improvement data were collected by the professionals of the Breakthrough Collaborative's teams. Measurements were derived from process and outcome indicators, developed by the national expert team to measure goal attainment on each of the SMART goals. Data were entered and processed in Excel by the local coordinators, who had received training to do so. Periodically, the local data were fed back to the teams for discussions and adaptation of improvement plans. Aggregation and analysis of all data was done by the expert team and data managers of the Trimbos Institute. To maintain privacy, patient data were made anonymous before being sent to be processed on a national level. In order to monitor the change over time, the team performances of process indicators were analysed as repeated measures of three-monthly data. Teams that collected data throughout the improvement year had four terms of 3 months to demonstrate change. Other teams, starting to collect data only later, may have produced just three sets of data. In addition to the improvement data, qualitative data were collected from the local team coordinators, in the last stage of the project. For this purpose, a questionnaire was used, with items on: characteristics of the team, results according to the coordinator, strengths and weaknesses of the improvement method, influencing factors, spread and consolidation of results. Seven coordinators, reporting on 10 out of 13 teams, returned the completed questionnaire.

- – A network of multidisciplinary teams

- – An expert team, teaching the stepped-care model

- – SMART goal setting, a set of indicators to monitor results and an Excel worksheet

- – A training for local team coordinators on the Breakthrough method and data collection

- – Four conference days for all improvement teams for exchange and learning

- – One conference day for local team coordinators for more intensive exchange with the expert team

- – Five meetings between local team coordinators, with the expert team present

- – Team visits of experts and national project coordinators

- – Telephone contact between local and national coordinators

- – Written feedback on improvement reports and data charts

- – A virtual network environment for exchange of best-practices, a Toolkit of instruments and treatment protocols, online discussions and links to relevant sites

- – A two-day training on problem solving treatment for professionals

- – A workshop workflow improvement

Table 2   Improvement strategies offered during the Depression Breakthrough Collaborative

5.3   Results

A total of 13 teams participated in the project, consisting of 101 professionals and 15 managers or staff. The teams all had a multidisciplinary character, including at least one or more general practitioners, and a psychiatrist or a psychotherapist working in a specialised Mental Health Organisation. In total, 39 general practitioners were involved, 14 primary care psychologists, 16 social workers, 11 specialised mental health nurses, 8 physiotherapists, 6 psychologists or psychotherapists and 7 psychiatrists. The smallest team consisted of 6 persons, the largest 15 members. The teams all had a local team coordinator, responsible for supporting the professionals, managing communications within the national network, and pushing the local improvement process forward. Most of the team coordinators were staff employees in primary care support organisations called Regional Support Structures (Regionale Ondersteuning Structuur, ROS). Five hundred and forty-three adult patients were registered by the 13 teams during the improvement year. The inclusion ranged from 17 patients in the team with the lowest patient number and 93 patients in the team with the highest. All teams selected their goals for improvement (see Table 1). SMART goals 1 and 2 were obligatory for all teams, goal 3 and 4 were selected by 10 teams, goal 5 was selected by four teams.

I What are we trying to accomplish?

II How will we know that a change is an improvement?

III What changes can we test that will result in an improvement?
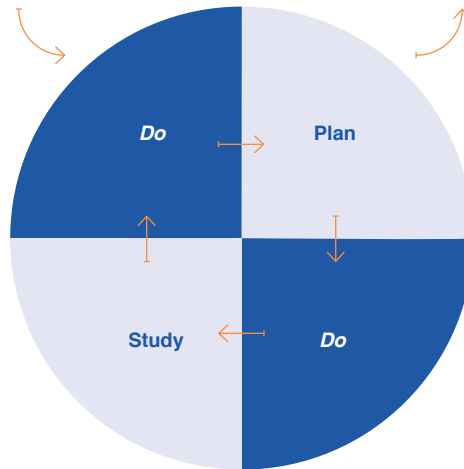
Plan phase: professionals decide the objective and the specific change to be tested and prepare a plan in terms of timing, people's roles, data to be collected et cetera.

Do phase: test of changes are carried out, observed and documented.

Study phase: data are analysed. Expected and unexpected results, positive or negative, are compared. Team members explicit what can be learned and decide about what to improve next.

Act phase: the team is ready to move to the next step up the improvement ramp. Should the idea being tested be abandoned or modified [Nelson et al. 2007; van Splunteren et al. 2003; Langley et al. 1996)?

Figure 2   The Nolan model for improvement

5.3.1 Diagnostic skills

General practitioners were asked to differentiate between severely depressed and non-severely depressed patients. The label severe depression was considered appropriate if the patient previously had depression symptoms lasting 6 months or longer, and/or showed an insufficient response to a former treatment and/or reported suicidal ideation, psychotic features or a high level of social malfunctioning. Out of the 543 patients registered during the project, 536 patients were diagnosed to have either non-severe or severe depressive symptoms (Figure 3). Overall 356 patients (66%) were considered non-severely depressed and 180 (34%) showed severe symptoms according to the general practitioners. Figure 3 also shows a large variability between the teams in the proportion of patients in each category, with the proportion of severely depressed patients ranging from 2% (team 12) to 83% (team 6). The team with the largest patient group (n=93) registered 76 non-severe depressed patients (82%) and 17 severe patients (18%).

5.3.2 Stepped-care approach

The overall goal of the improvement teams was the implementation of a stepped-care model, a depression care pathway with two levels of treatment intensity: a first step treatment level for patients with non-severe depression symptoms and a second step level for patients with severe depression symptoms (Figure 4).

The teams registered treatment data of a total of 514 patients, 346 (67%) patients with a non-severe depression and 168 (33%) patients with a severe depression. The overall mean percentage of the non-severe patient group receiving a first step treatment according to the stepped-care model was 78%, ranging from 53% in the worst performing team to 100% in three best performing teams. The mean percentage of the severely depressed patient group was 57%, ranging from 25 to 100% between the teams. The patient groups were extremely small in certain teams, thus accounting for these wide ranges. Although the scores in the non-severe group did not reach the level of 90%, there was a positive trend towards this target. This is in line with the reports of the local team coordinators, indicating that general practitioners did learn to offer patients with few or mild symptoms a brief or first step intervention instead of antidepressant treatment, once these first step interventions were made available in primary care. According to the stepped-care model, all patients with severe symptoms should have received psychotherapy or antidepressant treatment within 1 month, either in primary or in specialty care. Unfortunately, the improvement teams were not able to move good quality treatment for severely depressed patients close to the targeted 100%. In total 72 (43%) severely depressed patients did not receive antidepressant treatment or psychotherapy within 1 month or were offered treatment options of a too low intensity. This number includes 23 patients whom were referred to specialty care within 1 month, where they might have received proper treatment in time. The team coordinators indicated improvement in terms of a growing consciousness amongst professionals of the needs of severely depressed patients, better referral procedures and more attention to psychotherapy as an alternative for antidepressants.

5.3.3 Monitoring of depression symptoms

The professionals were asked to monitor depression symptoms with the BDI until recovery, defined as a BDI-score of 10 or lower. Table 3 shows that the teams succeeded in following around 70% of their patients during a period of 6 months. Repeated BDI monitoring by itself, was conceived to be very difficult to organise, especially since integration of the BDI measurements in existing ICT systems was lacking.

During the project, 477 patients received BDI monitoring at baseline, within 2 weeks after diagnosis. Four hundred and seventy-four patients (99%) scored more than 10, of whom 270 patients (57%) received a follow-up measurement within 3
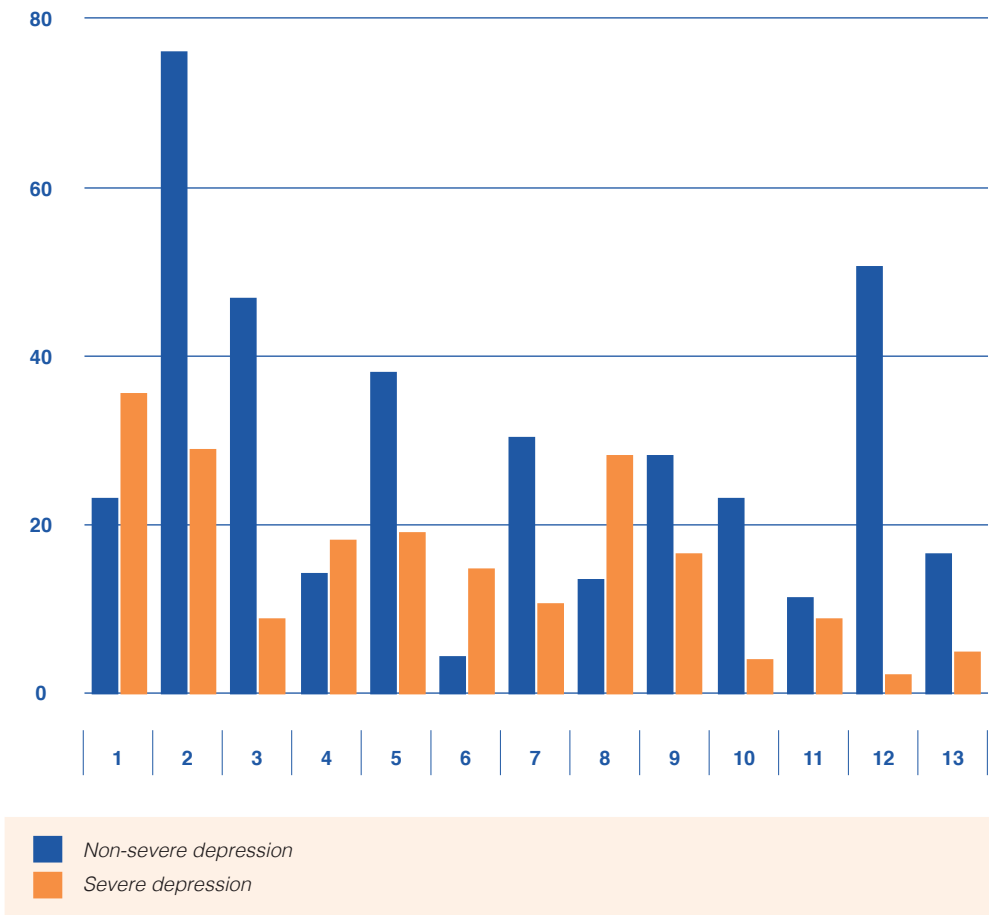
Figure 3   Number of severe and non-severe depression per team (n=536)

months. Of this group 76 persons (28%) had recovered according to the BDI score of 10 or lower. Of the 194 non-recovered patients, 103 patients had another follow-up measurement at 6 months (53%). Of this group, another 28 patients (27%) had recovered, 75 patients (73%) had a BDI score higher than 10.

Overall, 91 non-severely depressed and 50 severely depressed patients had BDI monitoring at baseline and within 3 to 6 months. Eighty-two percent non-severely

	Non-severely depressed patients (n = 91)	Severely depressed patients (n = 50)
Improved/recovered	75 (82%)/27 (30%)	44 (88%)/12 (24%)
Stable	3 (3%)	2 (4%)
Worse	13 (17%)	4 (8%)

Table 3   Depression symptoms at 6 months

depressed patients improved during that period, of whom 30% recovered and 17% of the patients worsened with increased scores on the BDI. Of the severely depressed group, 88% of the patients improved, 24% recovered and 8% patients worsened.

5.3.4 Collaboration and integration

In addition to the data, the comments of the team coordinators on the project were asked in a questionnaire. All team coordinators indicated that the project had a positive impact on collaboration within primary care. Professionals grew to know each other during the project, and as a consequence developed a mutual language on depression care, a better understanding of the content and added value of each of the different competencies and a more reliable collaborative relationship. This was a good basis for a regionally shared approach and responsibility in depression care. Teams also reported better collaboration in daily practice. Collaboration improved in terms of easier and faster consultation of a psychiatrist or psychologist when the patient's condition was unclear, better access to specialty care for primary care patients, and general practitioners staying better informed after referral. Improved collaboration was restricted to the professionals in the improvement teams, and did not really spread beyond this group.

5.3.5 Knowledge and guidelines

Another effect mentioned by the coordinators was improved knowledge of depression amongst the professionals and improved competence in terms of diagnosing and treating depressive symptoms. Some teams intensively discussed the guidelines at the start of the project, whereas other teams considered the Depression Breakthrough Collaborative as their knowledge base.

5.3.6 Strengths and weaknesses of the breakthrough method

The top-down goal setting appeared to be a success factor in primary care, general practitioners being in favour of practical tools, standards and clear instructions. Another successful element was the outcome monitoring using the BDI. Although hard to implement, it shifted the focus of professionals from their own clinical judgements to more objective results that could be shared with others. The Toolkit, describing the content of interventions in detail (number of sessions needed, topics to inform the patient about) served as a fidelity tool for correct development and implementation and as a basis for team discussions.

Weaknesses of the project, experienced by the team coordinators, were related to a mismatch between the project's design and the primary care working culture. PDSA cycles were hard to apply and did not fit into the existing culture of primary

care professionals, who were not used to discussing care processes and reflecting on results. Also the website, the main source of information and communication, was of no help to individual professionals, who were not used to virtual project environments. Other negative aspects of the project were the obligatory reports that needed to be sent to the national expert team and the changing planning of conference days and other happenings.

% of patients receiving first step treatment according to stepped care model
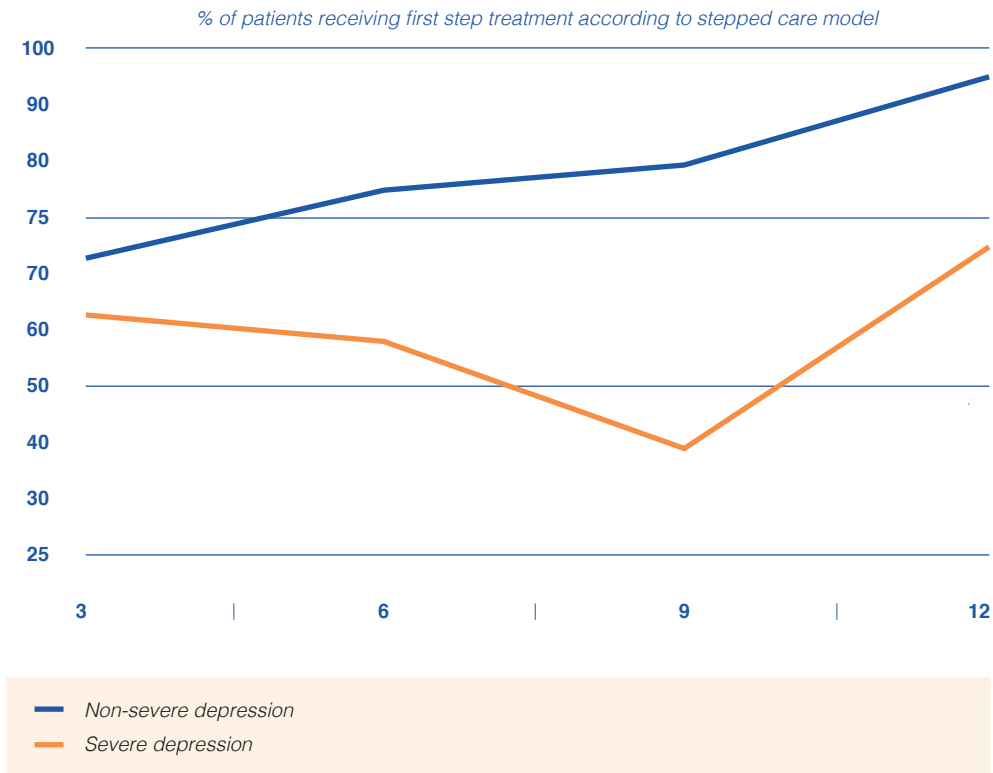
Figure 4   Percentage of patients receiving first step treatment according to stepped-care model

5.3.7 Influencing factors

Factors facilitating the project were: the presence of a strong local team coordinator, enthusiastic team members (particularly the general practitioner as the key player in the team), financial support for time spent on the project from an insurance company, and the embedment of the project within a broader quality improvement policy of the Mental Health Organisation or primary care health centre. Most of the local team coordinators were employed by the so-called Regional Support Structures, rather new organisations in Dutch primary care, created by the Ministry of Health to help professionals improve the quality of care.

Some of the healthcare insurance companies reimbursed general practitioners for the time spent on the project and paid for the team coordinator to support the team.

Factors hindering the project were: a lack of interest by the management, a lack of dedicated time for participating professionals, a lack of patients with new depression symptoms in primary care during the project, and the short length of the project's duration. Most teams felt the time frame of the project was too short for real change, especially in smaller teams, with only one general practitioner. Focusing on a longer change period and continuing improvement activities after the project's formal ending, was the way most teams dealt with these frustrations.

5.4 Discussion

Thirteen multidisciplinary teams participated in the quality improvement project. In total 101 care professionals were involved, and 536 patients were diagnosed. Overall 356 patients (66%) were considered non-severely depressed and 180 (34%) patients showed severe symptoms. The mean percentage of non-severe patients treated according to the model was 78%, and 57% for the severely depressed patient group. Compared to numbers mentioned in the literature of 23% of patients with anxiety and depression receiving the right treatment in primary care, this could be considered as relatively high (Fernandez, Haro, Martinez-Alonso, Demyttenaere, Brugha, Autonell et al. 2007). The proportion of non-severely depressed patients receiving the right first step treatment slightly improved during the project, but this was not the case for the severely depressed patients. The teams were able to monitor depression symptoms to a reasonable extent during a period of 6 months. Within 3 months, 28% of monitored patients had recovered, meaning a BDI score of 10 and lower, and another 27% recovered between 3 and 6 months. Collaboration between primary care and specialty care and within primary care improved but did not spread beyond the teams. The team coordinators indicated that a breakthrough, although still fragile, was being achieved in terms of professionals improving their knowledge of depression and depression guidelines, learning to use new and less intensive treatments in mild cases instead of antidepressant treatment and improving collaboration within and between the settings, so that access to specialty care for severely primary care improved.

In total, 39 practitioners identified 536 new cases, a mean of 14 patients per general practitioner. This is lower than expected, considering the national incidence rate of 24 patients in a general practice of 2,300 subscribed patients, suggesting that the general practitioners did not identify all patients with depression symptoms or did not include all patients who were identified (Braspenning, Schellevis & Grol 2004). The diagnostic performances suggest that the project served as a platform

for general practitioners to change their behaviour and start to differentiate between severe and non-severe depressive symptoms. Whether this was done in a reliable way, reflecting the true proportions, is not clear. The large variability between the general practitioners suggests that, apart from epidemiological differences, several professional related factors could have influenced the diagnosis. For instance, the sensitivity of some of the general practitioners to picking up on mild or early depression symptoms, and their ability to discuss their findings with the patient, could have been more or less developed. Also, a doctor feeling uncomfortable with a particular label and the corresponding treatment level could have adapted the treatment criteria to his own perception.

The monitoring indicators showed that the teams were able to monitor depression symptoms to a reasonable extent during the first 6 months of the treatment. This can be considered as a rather big improvement, considering the lack of routine, infrastructure and ICT support. When patients had stopped visiting the practices, possibly because of diminishing symptoms, continuous monitoring proved to be problematic.

The data suggest an improvement ramp pushing the quality of care for patients with non-severe depression forward. This in line with data from a previous Depression Breakthrough Collaborative that served as a pilot project. In that project, data of pre-collaborative treatment were compared to the improvement data, showing a very sudden drop in unnecessary antidepressant prescriptions for non-severely depressed patients from 61 to 11%, during the very first weeks of the collaborative (Franx, Spijker, Huyser & de Doelder 2006). In the current project, no pre-post trend can be shown, so nothing can be said about the actual change introduced during the collaborative.

The recovery rates are in line with the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, a naturalistic study showing that only one-third of patients achieves remission with initial treatment and that remission rates decline with successive treatment failures (Nelson 2006). The results of our project, although not based on research data, confirm the suggestion derived from the scientific research into collaboratives, showing modest effects on outcomes at best (Schouten, Hulscher, van Everdingen, Huijsman & Grol 2008).

Our project also builds on reports of other improvement work in depression care that show a positive impact on the quality of care and on patient outcomes. In the American version of the Depression Breakthrough Collaborative, the Chronic Care Model was implemented, also based on the assumption that depression care is fragmented and that there is a gap between guideline recommended and actual care (Katzelnick, Von Korff, Chung, Provost & Wagner 2005). The change concepts considered to be essential in the American project turned out to be establishing and maintaining a patient register, care coordination, diagnostic assessment and pro-active follow-up. Factors facilitating that project were: the support of

organisational leadership showing the essential role of the top management, and a small practice size (Katzelnick, Von Korff, Chung, Provost & Wagner 2005; Meredith, Mendel, Pearson, Wu, Joyce, Straus et al. 2006). Some of the essential change concepts show overlap with the positive experiences in our project concerning diagnostic assessment and pro-active follow-up. Still, the stepped-care approach, introducing different patient categories and corresponding treatment levels, with much attention to other than pharmacological approaches, can be considered distinctive and of relevance to international readership.

There are several limitations to this project. Firstly, registration of improvement indicators was hampered in various ways and the quality of data gathering during the project varied. Although some teams managed to collect most data for their patients, the overall database showed many missing values. A second limitation was the poor insight in the actual implementation of the interventions. The data are based on reports of the professionals; it is unclear whether patients actually received care according to the protocol or guidelines. Thirdly, the twelve months duration of the project; this may have been too short to measure any impact on the care processes.

It is clear that the information derived from these data does not pretend to serve as new, generalisable knowledge on causal mechanisms in health care, but as a mirror for reflection and discussion on processes of change in depression care. Quality improvement is a topic of interest to many managers and professionals in this sector, also stimulated by policy makers and insurance companies. Although changing depression care is on the agenda of many, the question of how to go about it is still unanswered. The data presented here may help to find some of the answers. Parallel to these quality improvement data, a quasi-experimental trial was conducted, comprising rigorous quantitative and qualitative process and outcome data-gathering on the patient, the professional and the team level, and a comparison between the collaborative study population and a care-as-usual group.

5.5 Conclusions

A stepped-care approach seems acceptable and feasible in primary care, introducing different levels of care for different patient groups. Although the Depression Breakthrough Collaborative introduced new treatment concepts in primary and specialty care, the change capacity of the method remains unclear. Thorough data gathering is needed to judge the real value of this intensive improvement project.

Chapter 6

Screening and guided self-help
intervention for anxiety and depression
in patients with type 2 diabetes.
A new role for diabetes nurses
in primary care?

Summary

Strategies for timely recognition and adequate treatment of mental disorder in diabetes are urgently needed. The aims of this study are to develop and evaluate an intervention for anxiety disorder and major depressive disorder (depression) in patients with type 2 diabetes (T2DM) by diabetes nurses (DNs) in primary care that requires minimal effort of all care professionals involved.

In this pilot, an open clinical study with pre-post test, seven trained DNs screened their patients. Patients screen-positive for anxiety disorder or depression underwent a standardised interview (MINI) by a researcher for validation. Patients fulfilling DSM-IV-TR criteria for anxiety disorder or depression were offered a self-help intervention supported and monitored by the DN in one-to-one guidance. Follow-up assessment was at six months.

Of 311 eligible patients, 111 consented to screening. Fifty-five patients were screened positive; 26 screen-positives were confirmed. Of the latter, 16 started and 15 completed the guided self-help intervention. Anxiety symptoms dropped 3.2 points (p=0.011), depression symptoms 5.7 points (p=0.007), and somatic symptom severity 2.9 points (p=0.041) on the Patient Health Questionnaire. Diabetes-related negative emotions (PAID-NL) dropped 3.8 points (p=0.048). The health profile (EuroQol) improved by 14 points (p=0.007), and emotional role-functioning (SF-36) showed 33.4 points improvement (p=0.010). To conclude, trained DNs succeeded in screening and guiding a self-help intervention; mental and somatic symptoms, the generic health profile, and quality of life improved significantly.

This pilot strongly indicates that DNs can perform screening and one-to-one guidance regarding a self-help intervention for anxiety disorder and depression, playing an important role in the early detection and follow up of co-morbid mental disorders complicating diabetes.

"The pleasure that is in sorrow is sweeter than the pleasure of pleasure itself."
Percy Bysshe Shelley, 1821, A Defence of Poetry

6.1 Introduction

Major depressive disorder (depression) is highly prevalent in patients with type 2 diabetes (T2DM) (Egede & Ellis 2010). Estimates of the prevalence of anxiety disorder are also high (Grigsby, Anderson, Freedland et al. 2002; Fisher, Skaff, Mullan et al. 2008). Both co-morbid anxiety and depression are associated with reduced well-being, functioning and quality of life, poor coping behaviour, decreased compliance and diabetes control, high HbA1c levels and more diabetes complications (Egede & Ellis 2010; Grigsby, Anderson, Freedland et al. 2002; Fisher, Skaff, Mullan et al. 2008). The importance of enabling diabetes patients through somatic and psychological well-being to improve self-management is well recognised (World Federation for Mental Health 2004; Singh 2008). In order to improve treatment, timely and adequate intervention should closely follow early recognition of symptoms, addressing not only diabetes-related distress, but also anxiety disorder and depression (Singh 2008; Pouwer, Beekman, Lubach et al. 2006).

In the Netherlands, as elsewhere in Europe, the rapidly growing prevalence of diabetes, along with the rising awareness of deficiencies (such as lack of care coordination, limited patient follow up over time, and inadequate support in self-management skills), calls for a transformation in diabetes care, and clear allocation of tasks and responsibilities of care professionals (World Health Organization 2008; Shah, Hux, Laupacis et al. 2007).

The role of the diabetes nurse (DN) is to provide education and support to people with diabetes and to help patients to self-manage their diabetes (EADV/AVVV 2004). In the Netherlands, DNs can be, but are not necessarily, educated as a nurse practitioner or specialised as a nurse specialist. DNs can be affiliated with a general practice, home care services, a healthcare centre or hospital. Early detection of mental disorder, followed by appropriate intervention or referral, fits the

professional profile of DNs and of all care professionals involved in diabetes care; as primary care managers of these patients, DNs are often the ones with the most frequent patient contact. When performed by the DN, these tasks would require minimal effort on the part of all of the care professionals involved and can be integrated into diabetes management, requiring little change in daily practice.

However, no specific tools for nurses are available and interventions focusing on co-morbid anxiety disorder and depression are not sufficiently integrated into diabetes care. Our research question concerned whether it is feasible for trained and equipped nurses to screen T2DM patients for co-morbid depression or anxiety disorder and support and monitor patients in following a self-help intervention, in collaboration with the general practitioner (GP).

The aims of this study are: (1) to develop an intervention targeting anxiety disorder and depression in patients with T2DM in primary care; and (2) to evaluate the effect of this intervention on mental health status, generic health profile and quality of life.

6.2 Patients and methods

6.2.1 Enrolment and screening of patients

The study was carried out with seven DNs working with 73 GPs in seven general practice settings or home care services located throughout the Netherlands, recruited by announcements in several nursing magazines and websites. Three DNs are additionally trained as a nurse practitioner, one as a nurse specialist. The DNs have on average 26 years (range=21) of experience as a registered nurse and six years (range=8) as a DN. Four DNs are directly affiliated with a general practice, and therefore know the patient's GP. Three DNs employed by home care services have no direct contact with the GP. DNs' main tasks concern: controlling patients' HbA1c, cholesterol, blood pressure, feet and waistline; adjusting the amount of insulin; and providing advice on lifestyle (diet, exercise). The total number of DNs working in each setting differs from one to six. The case-load varies from 125–3000 patients per year per setting.

T2DM patients aged 18 years and older, listed with general practices and home care services, and receiving care from participating DNs, were asked for their written informed consent to participate in this study. Patients already receiving mental health care, or diagnosed with dementia or psychosis, were excluded. All patients who met the inclusion criteria and signed informed consent were screened for anxiety disorder and depression by their DN.

The screening procedure strictly followed written instructions. The interview of Koeter & van den Brink (Koeter & van den Brink 1992) was used, an adaptation

of the Goldberg screen (Goldberg, Bridges, Duncan-Jones et al. 1988) with comparable predictive values (positive predictive value 56.5%; negative predictive value 100%; sensitivity 100%; specificity 84.2%) (Tiemens 1999). The altered algorithm improves time efficiency of the instrument while screening for both anxiety disorder and depression as defined by DSM-III. The screening needed about five minutes per patient.

Age, mean yrs (SD), range	58.5 (9.86) 40.1–80.6
Gender, % female (n)	93.3 (14)
Native country other than Netherlands, % (n)	20.0 (3)
Living situation, % (n)	
Married/living together	53.3 (8)
Living alone	46.7 (7)
Educational level, % (n)	
Low	46.7 (7)
Middle	40.0 (6)
High	13.3 (2)
Time since onset of T2DM, %(n)	
≤1 year	6.7 (1)
1-5 years	40.0 (6)
5-10 years	33.3 (5)
> 10 years	20.0 (3)
Somatic co-morbidity, no. of other chronic somatic diseases, % (n)	
1 disease	20.0 (3)
2 diseases	13.3 (2)
3 diseases	40.0 (6)
≥4 diseases	26.7 (4)

Table 1   Sociodemographic and medical data of patients completing the self-help intervention (n=15)

A researcher interviewed patients with positive screening outcomes using a standardised telephone interview, the MINI International Neuropsychiatric Interview (anxiety and depression sections), providing a classification for anxiety disorder or depression according to DSM-IV-TR criteria (Vliet, Leroy & van Megen 2000). Patients as thus classified were offered the self-help intervention and one-to-one guidance by the DN. Patients in need of more intensive treatment according to the MINI, and in the opinion of the GP, were considered non-eligible for this intervention.

Table 1 presents sociodemographic and medical data of those patients who received the guided self-help intervention.

6.2.2 Training programme for nurses

Participating DNs followed a training programme developed for this study, in four half-day sessions with six-week intervals. The trainers were a psychologist and a nurse (JM and GH). The learning goal of this training programme was to prepare the DNs for the screening and one-to-one guidance of their patients, and a follow-up procedure. The training comprised transferring knowledge and skills on diagnosis and treatment of anxiety and depressive disorder and co-occurrence with diabetes. Session one included: what are the symptoms of these disorders; how do these interact with diabetes and what are the consequences; how do you recognise these disorders; what type of treatments are available; and what can be the role of the diabetes nurse? Session 2 related to introducing and applying the screening instrument (including how to carry out the screening procedure strictly), and informing patients on screening results and follow-up intervention (using interviewing and feedback techniques); session 3 comprised introducing and applying the self-help intervention, and using coaching and motivational techniques for guiding patients one-to-one; and session 4 focused on adequate referral to the GP and a résumé of training. A follow-up meeting after two months provided a booster training session on supporting and monitoring patients.

Powerpoint presentations, a video recording of depressive elderly patients and role plays were used; printed material was supplied and explained verbally.

6.2.3 Guided self-help intervention

A work book was developed by adapting related bibliotherapy courses to the target group and using feedback of the participating nurses in this study (Meeuwissen & Cuijpers 2006). The work book gives patients insight into symptoms of anxiety and depression and dealing with diabetes as a chronic disease, and also trains the patient in healthy life-styles, relaxation techniques, thinking styles, assertiveness, social activities, and relapse prevention. Techniques from cognitive therapy, rational-emotive behavioural therapy, and social learning theory are used in a structured, stepwise approach, framing clear goals, and encouraging learning by practice with specific exercises.

6.2.4 One-to-one guidance by DNs

DNs guided patients one-to-one following a protocol, supporting and monitoring patients in following the self-help intervention (e.g. explaining how to use the self-help work book, discussing the material in the work book with the patient, and acting as a back-up if problems arose). To this end, patients had three to five sessions with the DN, which was an intensification of the normal frequencies of nurse visits (about once every two to three months) to a frequency of once every two to four weeks, during a period of at least six weeks and at most three months.

Additional tools were developed to equip DNs, including standardised referral letters to inform GPs about the patient, and psychoeducation material to hand out.

6.2.5 Follow-up procedure

Patients were referred to the GP by DNs if insufficient improvement of mental health status was achieved. All GPs agreed on treating patients according to current Dutch practice guidelines after referral by DNs.

A standardised procedure was initiated for patients with an increased suicide risk according to the MINI interview: one of the researchers informed the DN and GP by letter and telephone, and advised the GP to assess for suicide risk and mental disorder. If suicidal or in need of specific intervention, the patient was excluded from the guided self-help intervention and the GP monitored the patient.

6.2.6 Assessment and main variables measured

In this 18-month pilot – an open clinical study – baseline measurement was conducted by the researchers with patients included for the guided self-help intervention and follow-up measurement with completers done at six months. Mental health status was measured by the Patient Health Questionnaire (PHQ) (Spitzer, Kroenke, Williams, and the Patient Health Questionnaire Primary Care Study Group 1999). Diabetes-related negative emotions were assessed with the Problems Areas In Diabetes questionnaire (PAID-NL) (Snoek, Pouwer, Welch et al. 2000). Quality of life was measured by the SF-36 (McHorney, Ware & Raczek 1993), and the generic health profile by the EuroQol (EuroQol Group 1990). Medical data were retrieved from the patient record, reported by the DNs.

For process evaluation, DNs were interviewed face-to-face and GPs by telephone in a semi-structured interview.

The study protocol received full ethical approval from the medical ethics committee, METIGG.

6.2.7 Analysis methods and statistics

Descriptive statistics for sociodemographic variables and medical data were used. The McNemar test was used to compare categorical outcome measures. The Wilcoxon signed rank test, a non-parametric variant of the paired t-test, was used for continuous variables. Spearman's rho was used to test for correlations of baseline scores of the physical component score on the SF-36 with baseline scores and difference scores on the PHQ and the PAID-NL.

6.3 Results

6.3.1 Screening results

Figure 1 shows the flow chart of patients. Screening resulted in 49.5% screen positives of whom 49.1% truly had an anxiety disorder (n=7), depression (n=6), or both (n=13), as validated by MINI interview.

6.3.2 Effects on mental health status

The results are presented in Table 2. The mean PHQ score for anxiety symptoms was reduced significantly, from moderate 10.4 to mild 7.2 (p=0.011) after intervention, as well as the mean score for depression symptoms, from moderately severe 15.7 to moderate 10.0 (p=0.007). Most patients decreased one or more levels in depression severity (66.7%; n=10). For anxiety symptoms, no severity levels are available but 73.3% of patients improved in symptoms (n=11).

The mean PHQ score for somatic symptom severity, although remaining medium, reduced significantly from 14.8 to 11.9 (p=0.041). The percentage of patients whose somatic symptom severity decreased one or more levels was 40.0% (n=6). In addition, diabetes-related emotional distress on the PAID-NL was reduced significantly after intervention, from 24.7 to 20.9 (p=0.048). The percentage of patients whose emotional distress decreased one or more levels was 40.0% (n=6).

Eleven patients (73.3%) showed improvement in at least one measure while remaining the same for all other measures of mental health status.

6.3.3 Effects on health profile and quality of life

The health profile improved after intervention, as indicated by the EuroQol EQ-5D scores (Table 2), specifically in the areas of usual activities or related to anxiety or depression. A significantly improved self-rated health was shown by a raised score on the Visual Analogue Scale, from 44.7 to 58.7 (p=0.007), indicating a higher quality of life.

Health-related quality of life also improved significantly on the SF-36 role scales: from 8.3 to 48.3 for the physical role (p=0.007), and from 24.4 to 57.8 for the emotional role (p=0.010), as well as on the mental health scale (p=0.003). The SF-36 mental component score also improved significantly (p=0.020); the SF-36 physical component score (PCS) did not change significantly (p=0.191). We did not find any significant correlations between the baseline scores of the PCS with PHQ and PAID-NL baseline scores or difference scores.

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┌────────────────────────────────┐
│ Approached: n = 311            │
└────────────────────────────────┘
                │                        ┌──────────────────────────────────────┐
                │───────────────────────▶│ No informed consent: n = 188         │
                ▼                        └──────────────────────────────────────┘
┌────────────────────────────────┐
│ Informed consent: n = 123      │
└────────────────────────────────┘
                │                        ┌──────────────────────────────────────┐
                │───────────────────────▶│ Excluded: n = 3                      │
                │                        │ Language problems: n = 2             │
                │                        │ Already in treatment: n = 1          │
                │                        └──────────────────────────────────────┘
                │                        ┌──────────────────────────────────────┐
                │───────────────────────▶│ Loss to follow up: n = 9             │
                │                        │ Drop-out nurse: n = 9                │
                ▼                        └──────────────────────────────────────┘
┌────────────────────────────────┐
│ Screened n = 111               │
└────────────────────────────────┘
                │                        ┌──────────────────────────────────────┐
                │───────────────────────▶│ Excluded screen negatives: n = 56    │
                ▼                        └──────────────────────────────────────┘
┌────────────────────────────────┐
│ Screen positives: n = 55       │
└────────────────────────────────┘
                │                        ┌──────────────────────────────────────┐
                │───────────────────────▶│ Loss to follow up: n = 2             │
                │                        │ Logistic reason: n = 2               │
                ▼                        └──────────────────────────────────────┘
┌────────────────────────────────┐
│ MINI interviewed n = 53        │
└────────────────────────────────┘
                │                        ┌──────────────────────────────────────┐
                │───────────────────────▶│ Excluded: n = 27                     │
                │                        │ MINI negative                        │
                ▼                        └──────────────────────────────────────┘
┌────────────────────────────────┐
│ MINI positives n = 26          │
└────────────────────────────────┘
                │                        ┌──────────────────────────────────────┐
                │───────────────────────▶│ Excluded: n = 7                      │
                │                        │ Specific phobia only: n = 1          │
                │                        │ High suicide risk: n = 5             │
                │                        │ Low suicide risk, complex problems: n = 1 │
                ▼                        └──────────────────────────────────────┘
┌────────────────────────────────┐
│ Baseline measurement ($T_0$): n = 19 │
└────────────────────────────────┘
                │                        ┌──────────────────────────────────────┐
                │───────────────────────▶│ Loss to follow up: n = 3             │
                │                        │ Died: n = 1                          │
                │                        │ Drop-out: n = 2                      │
                ▼                        └──────────────────────────────────────┘
┌────────────────────────────────┐
│ Intervention: n = 16           │
└────────────────────────────────┘
                │                        ┌──────────────────────────────────────┐
                │───────────────────────▶│ Loss to follow up: n = 1             │
                │                        │ Drop-out: n = 1                      │
                ▼                        └──────────────────────────────────────┘
┌────────────────────────────────┐
│ Follow-up measurement ($T_1$): n = 15 │
└────────────────────────────────┘
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Figure 1   Patient flow chart

6.3.4   Process evaluation

The mean level of self-perceived knowledge of participating DNs about anxiety and depression increased from 4 to 7 on a 10-point scale after training. Prior to training, most DNs lacked experience in coaching and motivational interviewing techniques; all DNs experienced problems in applying a pre-structured interview protocol. Therefore, more time than initially planned was used to instruct and practise the screening procedure.

Five DNs had patients eligible for the self-help intervention, one to six patients per DN; one patient dropped out. Patients visited the DN on average four times. Two patients were referred after completing the self-help intervention due to remaining symptoms.

Overall, DNs considered the screening procedure and one-to-one guidance feasible and applicable.

GPs with DNs directly affiliated, or having more than one patient with guided self-help intervention, were the most positive about screening and follow up by the DN and about implementation of the intervention in their practice.

	Baseline	Follow-up	P-value
Health Status: PHQ[a]			
Depression (sum score)[b], mean (SD), range	15.7 (7.7), 5.0-26.0	10.0 (7.7), 0.0-19.0	0.007*
Depression severity level, % (n)			
None/minimal (0-4)	0.0 (0)	33.3 (5)	
Mild (5-9)	33.3 (5)	6.7 (1)	
Moderate (10-14)	13.3 (2)	13.3 (2)	
Moderate Severe (15-19)	13.3 (2)	46.7 (7)	
Severe (20-27)	40.0 (6)	0.0 (0)	
Anxiety disorder (sum score)[b],[†], mean (SD), range	10.4 (2.9), 6.0-14.0	7.2 (4.8), 0.0-14.0	0.011*
With panic disorder, % (n)[c]	26.7 (4)	6.7 (1)	0,250
Somatic symptom severity (sum score)[b], mean (SD), range	14.8 (5.8), 4.0-24.0	11.9 (5.8), 3.0-21.0	0.041*
Severity level, % (n)			
None/minimal (0-4)	6.7 (1)	6.7 (1)	
Low (5-9)	6.7 (1)	33.3 (5)	
Medium (10-14)	26.7 (4)	20.0 (3)	
High (15-30)	60.0 (9)	40.0 (6)	
Diabetes-related negative emotions: PAID-NL[d]			
Diabetes-related distress[b], mean (SD), range	24.7 (21.1), 6.0-78.0	20.9 (24.3), 0.0-75.0	0.048*

Health profile: EuroQol EQ-5D							
Visual Analogue Scale[b,e], mean (SD), range	44.7 (21.1), 7-80			58.7 (18.3), 20.0–87.0			0.007*

Problem areas (none, some, extreme problems), % (n)	**None**	**Some**	**Extreme**	**None**	**Some**	**Extreme**	
Mobility	46.7 (7)	46.7 (7)	6.7 (1)	73.3 (11)	20.0 (3)	6.7 (1)	
Self-care	80.0 (12)	13.3 (2)	6.7 (1)	80.0 (12)	13.3 (2)	6.7 (1)	
Usual activities	13.3 (2)	66.7 (10)	20.0 (3)	33.3 (5)	46.7 (7)	20.0 (3)	
Pain/discomfort	13.3 (2)	46.7 (7)	40.0 (6)	53.3 (8)	13.3 (2)	33.3 (5)	
Anxiety/depression	6.7 (1)	73.3 (11)	20.0 (3)	66.7 (10)	33.3 (5)	0.0 (0)	

Quality of life: SF-36[e]		
Roles[b], mean (SD), range		
Physical functioning	46.7 (26.6), 0.0-80.0	53.0 (29.9), 0,0-95.0	0.132
Role - physical	8.3 (20.4), 0.0-75.0	48.3 (47.7), 0.0-100.0	0.007*
Bodily pain	40.1 (24.6), 0.0-87.8	52.1 (29.9), 0.0-100.0	0.090
General health	43.0 (14.2), 20.0-80.0	44.7 (14.1), 20.0-65.0	0.342
Vitality	34.7 (15.5), 10.0-65.0	44.7 (26.8), 5.0-95.0	0.074
Social functioning	48.3 (30.9), 0.0-100.0	53.3 (35.5), 0.0-100.0	0.559
Role - emotional	24.4 (38.8), 0.0-100.0	57.8 (44.5), 0.0-100.0	0.010*
Mental health	41.9 (13.8), 16.0-64.0	61.3 (22.3), 20.0-100.0	0.003*
Relative health	41.7 (29.4), 0.0-100.0	51.7 (25.8), 0.0-100.0	0.218
Mental component socre[b], mean (SD), range	31.8 (9.8), 17.9-52.7	41.0 (14.0), 20.8-61.4	0.020*
Physical component socre[b], mean (SD), range	36.0 (9.4), 21.9-53.9	38.6 (11.7), 15.3-60.6	0.191

*[a] Higher score indicates more symptomatology; [b] Wilcoxon signed rank test; [c] McNemar test; [d] Higher score indicates more distress; [e] Higher score indicates higher quality of life; * p<0.05; [†] n=14*

Table 2 **Health status, diabetes-related emotional distress, health profile, and quality of life at baseline and at 6 months follow up (n = 15)**

6.4 Discussion

This pilot strongly indicates that it is feasible for DNs to perform screening and or adequate referral. DNs adhered to the guidance protocol, whereas patients complied with the guided self-help intervention, including nurse visits, or with referral advice. Screening and guided self-help intervention resulted in improved patient outcomes. Mental health status significantly improved, as well as the health profile and quality of life, while diabetes-related negative emotions significantly reduced.

This pilot has several limitations. A limitation in the study design is that there was no control group. It is possible that purely the increased frequency of nurse contact

was the active ingredient that achieved the positive effects shown. Evidently, a randomised controlled trial conducted in a larger population is needed in order to establish robust effects, accounting for spontaneous recovery or effects resulting purely by increased nurse contact.

Furthermore, the applied screening instrument did not show a good positive predictive value. Given that nurses can be trained in applying other screening instruments as well, there is a need for alternative screening instruments that can be used efficiently and with a better positive predictive value. For example, a validation study of the PHQ-9 as a screening instrument for co-morbid depression in patients visiting diabetes out-patient clinics found a cut-off point of a summed score of 12 on the PHQ-9, resulting in a sensitivity of 75.7% and a specificity of 80.0% (van Steenbergen-Weijenburg, de Vroege, Ploeger et al. 2010).

Moreover, in this study focusing on mental disorder instead of milder problems, we found not only a high prevalence of anxiety and depressive disorder, which is consistent with prior research, but also a relatively high number of patients with suicide risk or severe disorder, leaving fewer patients to include in the self-help intervention. Nevertheless, the effects in this small group of patients were strong enough to show significant improvement. Also, SF-36 scores were very low compared both to the Dutch general population and to patients in general practice diagnosed with T2DM (Nationaal Kompas Volksgezondheid 2011; Adriaanse, Dekker, Spijkerman et al. 2004). Whether the study group represents only more difficult cases – for example, the number of co-morbid chronic somatic illnesses is high in our study group – or whether participating DNs are treating mainly more complex or severe cases, remains unknown. The severity of the physical status may affect mental health status; however, we did not find significant correlations between the SF-36 physical component score and mental health status.

This study demonstrates that introducing and embedding a screening procedure with follow-up intervention requires only small changes in diabetes primary care, and that expanding the role of DNs with these tasks requires relatively little training for diabetes nurses. In routine daily practice, screening could be fitted in with check-ups on a regular basis for those patients seen by DNs who are already aware of their individual circumstances and health-related problems. The standardised intervention developed in this study, addressing a disease management approach, could become part of regular diabetes training programmes. This study emphasises the key role that nurses can play in early detection and follow up of co-morbid mental disorders which complicate diabetes care, and in establishing improved patient outcomes. The positive findings of this pilot warrant further research into the efficacy of screening and self-help intervention guided by DNs.

Part III
The effectiveness of depression care management and the cost-utility of stepped care

Chapter 7

Meta-analysis and meta-regression analysis explaining heterogeneity in outcomes of chronic care management for patients with depression: implications for person-centered mental health care

Summary

Rationale, aims and objectives. Chronic care management programmes for depression show variation in effectiveness. This study aims to examine the clinical diversity and methodological heterogeneity related to the effectiveness of such programmes and to explain the heterogeneity in clinical outcomes. Objectives are to enable the understanding of and the decision making about depression management programmes and to contribute to the implementation of chronic care management strategies for depression as part of advances in person-centered mental health care.

Method. We performed a systematic review of reviews and empirical studies, including meta-analyses and meta-regression analyses on the most frequently reported outcomes. We explored to what extent the observed heterogeneity can be explained by study quality, length of follow-up, number of components of the Chronic Care Model (CCM) and patient characteristics.

Results. Pooled effects of depression management programmes show significant improvement in treatment response (RR=1.38; p<0.05) and treatment adherence (RR=1.36; p<0.05). In meta-regression analysis, study quality and depression severity explain the substantial heterogeneity in respectively treatment response (36.6%; p=0.0352) and treatment adherence (88.7%; p=0.0083).

Conclusions. The observed heterogeneity in depression outcomes cannot be explained by the number of intervention components and length of follow-up. Yet, the heterogeneity in treatment response can be explained partly by study quality, demonstrating the importance of good quality studies. Heterogeneity in treatment adherence can be explained partly by severity of the depression, indicating that taking account of depression severity contributes to maximising the effectiveness of chronic care management. Other potential sources of heterogeneity should be investigated to support informed decision making on treating depression as a chronic condition as part of person-centered health care.

"It's far more important to know what person the disease has than what disease the person has."

Hippocrates, c. 400 B.C.

7.1 Introduction

Depressive disorder (depression) is a major cause of chronic morbidity and disability throughout the world, representing an enormous and growing burden on individuals, families and societies by its impact on quality of life, social participation, health resource utilisation and productivity (Bromet, Andrade, Hwang, Sampson, Alonso, Girolamo et al. 2011; Lopez & Mathers 2006; Üstün, Ayuso-Mateos, Chatterji, Mathers & Murray, 2004; Murray & Lopez 1997). Depression, like other chronic conditions, poses main challenges to healthcare systems of many countries (Bodenheimer & Fernandez 2005; Institute of Medicine, IOM, 2001; World Health Organization 2008). Gaps exist between what is known as appropriate care for depression and the care patients actually receive (World Health Organization 2008). Quality deficiencies include a lack of coordination of care, insufficient compliance or adherence with evidence-based practice guidelines and limited symptom monitoring, evaluating of treatment outcomes and adjusting depression management accordingly (Bodenheimer, Wagner & Grumbach 2002; Bodenheimer, Wagner & Grumbach 2002; Wagner, Austin & Von Korff 1996; Wagner, Austin, Davis, Hindmarsh, Schaefer & Bonomi 2001; Wagner 1998; World Health Organization 2001; World Health Organization/World Organization of Family Doctors 2008). New strategies for providing depression care, that concern achieving long-term remission, improving health status and quality of life, and preventing recurrence of acute or new episodes of depression, are as diverse as the healthcare systems in which they are implemented (World Health Organization/World Organization of Family Doctors 2008; Singh 2008; Greβ, Baan, Calnan, Dedeu, Groenewegen, Howson et al. 2009; Nolte, Knai & McKee 2008; Hofmarcher, Oxley & Rusticelli 2007; Katon & Guico-Pabia 2011).

The Chronic Care Model (CCM), that has been adopted by the World Health Organization, summarises the basic components necessary for the provision of high-quality chronic care: self-management support (SMS), delivery system design

(DSD), clinical information systems (CIS) and decision support (DS) (Wagner, Austin, Davis, Hindmarsh, Schaefer & Bonomi 2001; Wagner 1998). Programmes based on the CCM capture a combination of components to accomplish productive interactions between informed activated patients and prepared and proactive practice teams to improve chronic care management (Coleman, Austin, Brach & Wagner 2009).

The inherently multi-component nature of chronic care management programmes implies that type, number and combination of included intervention components vary between studies. As yet, little is known about what elements of these programmes are essential in establishing effectiveness (Bower, Gilbody, Richards, Fletcher & Sutton 2006). Evidence for the impact of chronic care management for depression is characterised by a high level of statistical heterogeneity, with intervention effects being more different from each other than one would expect on the basis of chance alone (Coleman, Austin, Brach & Wagner 2009; Bower, Gilbody, Richards, Fletcher & Sutton 2006; Scott 2009; Mattke, Seid & Ma 2007; Congressional Budget Office 2004). This statistical heterogeneity can be caused by clinical diversity (e.g., variation in participants or outcomes studied) and methodological diversity (e.g., differences in length of follow-up or study design) (Coleman, Austin, Brach & Wagner 2009). This heterogeneity limits the insight into the effectiveness of depression management and revisiting the current literature is needed to support the decision making on chronic care management strategies.

The aim of this review is: i) to give an overview of evaluations of the effect of chronic care management for depression, showing heterogeneity in outcomes; and ii) to assess the extent to which differences in outcomes between studies of depression care management can be explained by differences in either of the following factors: (1) methodological study quality; (2) length of follow-up; (3) number of included intervention components according to the CCM; and (4) population characteristics. Meta-analyses and meta-regression analyses are performed to determine the pooled effects of interventions on different outcomes and to investigate potential sources of heterogeneity. By explaining the heterogeneity in outcomes, we aim to support decision making by policy-makers and programme planners on how to improve depression care and to contribute to the implementation of chronic care management strategies for depression.

7.2 Methods

7.2.1 Literature searches

Electronic database searches for English language systematic reviews and meta-analyses published between 1995 and 2009 were conducted in Medline. We

applied the same search strategy as in our systematic reviews on the effectiveness of chronic care management for COPD, diabetes and heart failure (Drewes, Steuten, Lemmens, Baan, Boshuizen, Elissen et al. 2012; Elissen, Steuten, Lemmens, Drewes, Lemmens, Meeuwissen et al. 2012; Lemmens, Lemmens, Boom, Drewes, Meeuwissen, Steuten et al. 2011). We combined the Medical Subject Headings (MeSH) 'patient care team', 'patient care planning', 'primary nursing care', 'case management', 'critical pathways', 'primary healthcare', 'continuity of patient care', 'guidelines', 'practice guideline', 'disease management', 'comprehensive healthcare' and 'ambulatory care' and text words 'disease state management', 'disease management', 'integrated care', 'coordinated care' and 'shared care' in combination with the MeSH term 'depressive disorder'. The references from each of the included reviews were hand-searched for potentially relevant empirical studies.

7.2.2 Study inclusion and data extraction

Systematic reviews or meta-analyses were included when these focused on: 1) depression as the main condition of interest; 2) patients aged 18 years or over as the main receivers of the interventions; 3) interventions consisting of at least 2 components of the CCM (Wagner, Austin, Davis, Hindmarsh, Schaefer & Bonomi 2001). To investigate heterogeneity in results, the primary studies underlying the reviews were obtained for further analysis if these satisfied the inclusion criteria mentioned above. Case reports and expert opinions were excluded. Studies published before 1995 were excluded, as it was not until 1995 before disease management appeared frequently in the medical literature (Coleman, Austin, Brach, Wagner 2009; Norris, Glasgow, Engelgau, O'Conner & McCulloch 2003). Two members of the research team (JM and LL) independently screened citations and extracted data, using separate forms for systematic reviews and primary studies. Disagreements were few and were resolved by consensus or a third reviewer (HD).

Data extracted from systematic reviews include: 1) method of data-synthesis (i.e., descriptive or meta-analysis); 2) number of studies included (total and specified by research design); 3) in- and exclusion criteria; 4) theoretical framework underpinning the chronic care programme of interest; 5) programme components (i.e., SMS; DSD; CIS; DS); 6) primary and secondary endpoints; 7) methods of the meta-analysis, if applicable (i.e., random or fixed effect model and assessment of heterogeneity); 8) effect sizes and explained heterogeneity, if applicable and 9) author's conclusion. Data extracted from primary papers include: 1) study design; 2) length of follow-up; 3) sample size; 4) in- and exclusion criteria; 5) mean or median age of included sample; 6) percentage males; 7) disease severity; 8) study setting (i.e., community; primary, secondary or tertiary care or combination thereof); 9) intervention, including programme components (i.e., SMS; DSD; CIS; DS); 10) control intervention; 11) process and outcome measures.

When important data were missing, we tried to retrieve these data from the authors. When unavailable, these data were not included in the analyses.

7.2.3 Assessing sources of heterogeneity

Based on the existing literature (see Discussion), we a priori identified potential sources of statistical heterogeneity between the studies: methodological quality, length of follow-up, number of included intervention components of the CCM and patient characteristics in the study population.

We applied the Technology Assessment-Disease Management instrument (HTA-DM), a validated and tailor-made instrument that has proven to measure reliably the methodological quality of health technology assessments of disease management. We used this instrument to categorise studies according to their quality, classifying studies as demonstrating either poor (<50 points), moderate (50 to 69 points) or good quality (70 to 100 points) (Steuten, Vrijhoef, Merode, Severens & Spreeuwenberg 2004).

Length of follow-up was measured as the mean number of months in the follow-up period. For the purpose of meta-analysis, this variable was dichotomised (<1 year, ≥1 year); in the meta-regression, length of follow-up was included as a continuous variable (number of months).

To assess chronic care programs for depression according to the 4 basic elements of the CCM, we followed the coding method of Zwar et al. (Zwar, Harris, Griffiths, Roland, Dennis, Powell Davies et al. 2006), using the most recent description of the model's components by Wagner et al. (Wagner, Austin, Davis, Hindmarsh, Schaefer & Bonomi 2001). Thus, self-management support (SMS) was described as supporting patients to manage their condition such as by routinely assessing progress or education; delivery system design (DSD) was described as the organisation of providing care such as planned visits or other roles or teams; clinical information systems (CIS) are described as the using of information systems to capture and use critical information like reminders, feedback on performance and registries for planning care; and decision support (DS) was described as the integration of evidence-based clinical guidelines into practice by reminder system, feedback system et cetera.

Patient characteristics in the study population were, if applicable, summarised as either minor or major depression, first or recurrent episode, younger or older age group and veteran or not.

7.2.4 Data analyses

Data collected from reviews were analysed descriptively; data gathered from primary studies were in addition meta-analysed to predict the differences in mean

changes in process and outcome measures between intervention and control groups over time. An a priori decision was made to meta-analyse, when possible, the 4 most frequently reported measures of either processes or outcomes of depression care.

When data were reported incompletely, for example when only mean score differences, odds ratios, fractions or figures instead of actual values are given or when these are not given for the control group, these data were requested from the authors. In the case of no response and where calculated estimations were impossible, the studies were excluded from the meta-analysis.

Review Manager (RevMan 5.0.2; The Cochrane Collaboration) was used to compute the pooled overall effects and the pooled effects for the subgroups of the 4 factors, that is, quality of study (poor, moderate or good), length of follow-up (less than 1 year or longer), number of components (2, 3 or 4) and patient characteristics (minor or major depression, first or recurrent episode, younger or older age group and veteran or not). Pooled risk ratios and 95% confidence intervals for dichotomous outcomes were analysed with the Mantel-Haenszel method using the random effect model and pooled mean differences and confidence intervals for continuous outcomes with the random model of Der-Simonian and Laird (Lipsey & Wilson 2001).

The suggested associations by the subgroup analyses were tested by meta-regression analysis. To identify to what extent the heterogeneity in outcomes can be explained by the quality of the studies, the length of follow-up, the number of components and patient characteristics, meta-regression analysis was performed if at least 8 studies could be included in the analyses. In contrast with the subgroup analyses, all factors were included as continuous variables in this meta-regression analysis, if possible. The effect sizes of primary studies were weighted using the inverse variance weight formulas (Lipsey & Wilson 2001) and imported together with the 4 factors as co-variates into the SAS statistical package (Proc Mixed, version 9.2) (Houwelingen, Arends & Stijnen 2002). The extent to which the 4 factors (co-variates) on the study level explained the variance in measured effects between studies was examined by fitting of univariable meta-regression models (Thompson & Higgins 2002). The relative decrease of the between study variance in the univariable model compared to an intercept only model is interpreted as the percentage of heterogeneity explained.

7.3 Results

7.3.1 Results of the search strategy

Eleven systematic reviews (Badamgarav, Weingarten, Henning, Knight, Hasselblad, Gano et al. 2003; Christensen, Griffiths, Gulliver, Clack, Kljakovic

& Wells 2008; Frederick, Steinman, Prohaska, Satariano, Bruce, Bryant et al. 2007; Gensichen, Beyer, Muth, Gerlach, Von Korff & Ormel 2006; Gilbody, Whitty, Grimshaw & Thomas 2003; Gilbody, Bower, Fletcher, Richards & Sutton 2006; Gilbody, Bower & Whitty 2006; Neumeyer-Gromen, Lampert, Stark & Kallischnigg 2004; Pirraglia, Rosen, Hermann, Olchanski, Neumann 2004; Vergouwen, Bakker, Katon, Verheij & Koerselman 2003; Williams, Gerrity, Holsinger, Dobscha, Gaynes & Dietrich 2007) and 42 studies reported in 45 papers (Adler, Bungay, Wilson, Pei, Supran, Peckham, Cynn et al. 2004; Araya, Rojas, Fritsch, Gaete, Rojas, Simon & Peters 2003; Arthur, Jagger, Lindesay & Matthews 2002; Aubert, Fulop, Xia, Thiel, Maldonato & Woo 2003; Blanchard, Waterreus & Mann 1999; Brown, Shye, McFarland, Nichols, Mullooly & Johnson 2000; Bruce, Have, Reynolds, Katz, Schulberg, Mulsant et al. 2004; Capoccia, Boudreau, Blough, Ellsworth, Clark, Stevens et al. 2004; Ciechanowski, Wagner, Schmaling, Schwartz, Williams, Diehr et al. 2004; Cuijpers & van Lammeren 2001; Datto, Thompson, Horowitz, Disbot & Oslin 2003; Dietrich, Oxman, Williams, Schulberg, Bruce, Lee et al. 2004; Dobscha, Corson, Hickam, Perrin, Kraemer & Gerrity 2006; Finley, Rens, Pont, Gess, Louie, Bull et al. 2003; Flaherty, McBride, Marzouk, Miller, Chien, Hanchett et al. 1998; Fortney, Pyne, Edlund, Williams, Robinson, Mittal et al. 2007; Goldberg, Wagner, Fihn, Martin, Horowitz, Christensen et al.1998; Hedrick, Chaney, Felker, Liu, Hasenberg, Heagerty et al. 2003; Hunkeler, Meresman, Hargreaves, Fireman, Berman, Kirsch et al. 2000; Jarjoura, Polen, Baum, Kropp, Hetrick & Rutecki 2004; Katon, Von Korff, Lin, Walker, Simon, Bush et al. 1995; Katon, Robinson, Von Korff, Lin, Bush, Ludman et al. 1996; Katon, Rutter, Ludman, Von Korff, Lin, Simon et al. 2001; Katon, Russo, Von Korff, Lin, Simon, Bush et al. 2002; Katzelnick, Simon, Pearson, Manning, Helstad, Henk et al. 2000; Lin, Simon, Katon, Russo, Von Korff, Bush et al. 1999; Lin, Von Korff, Russo, Katon, Simon, Unützer et al. 2000; Llewellyn-Jones, Baikie, Smithers, Cohen, Snowdon, Tennant 1999; Mann, Blizard, Murray, Smith, Botega, MacDonald et al. 1998; Miranda, Chung, Green, Krupnick, Siddique, Revicki et al. 2003; Oslin, Sayers, Ross, Kane, Have, Conigliaro et al. 2003; Peveler, George, Kinmonth, Campbell & Thompson 1999; Pyne, Rost, Zhang, Williams, Smith & Fortney 2003; Rickles, Svarstad, Statz-Paynter, Taylor & Kobak 2005; Rollman, Hanusa, Lowe, Gilbert, Kapoor & Schulberg 2002; Rost, Nutting, Smith, Werner & Duan 2001; Sherbourne, Wells, Duan, Miranda, Unützer, Jaycox et al. 2001; Simon, Von Korff, Rutter & Wagner 2000; Simon, Ludman, Tutty, Operskalski & Von Korff 2004; Solberg, Fischer, Wei, Rush, Conboy, Davis et al. 2001; Swindle, Rao, Helmy, Plue, Zhou, Eckert et al. 2003; Trivedi, Rush, Crismon, Kashner, Toprac, Carmody et al. 2004; Unützer, Rubenstein, Katon, Tang, Duan, Lagomasino et al. 2001; Unützer, Katon, Callahan, Williams, Hunkeler, Harpole et al. 2002; Worrall, Angel, Chaulk, Clarke & Robbins 1999) were identified that met the inclusion criteria. Of these, 4 studies report on 2 study arms (Brown, Shye, McFarland, Nichols, Mullooly & Johnson 2000; Goldberg, Wagner, Fihn, Martin, Horowitz, Christensen et al. 1998; Miranda, Chung, Green, Krupnick, Siddique, Revicki et al. 2003; Simon, Ludman,

Tutty, Operskalski, Von Korff 2004), that were treated as separate studies in the analyses. This results in a total of 46 primary studies (Figure 1).

Four of the included systematic reviews also performed a meta-analysis (Badamgarav, Weingarten, Henning, Knight, Hasselblad, Gano et al. 2003; Christensen, Griffiths, Gulliver, Clack, Kljakovic & Wells 2008; Frederick, Steinman, Prohaska, Satariano, Bruce, Bryant et al. 2007; Gensichen, Beyer, Muth, Gerlach, Von Korff & Ormel 2006; Gilbody, Bower, Fletcher, Richards & Sutton 2006; Gilbody, Bower, Whitty 2006; Neumeyer-Gromen, Lampert, Stark & Kallischnigg 2004). The number of studies included in the reviews varies from 9 to 82, with a median of 19 studies.

The set of primary papers included 36 randomised controlled trials (RCT) (Adler, Bungay, Wilson, Pei, Supran, Peckham, Cynn et al. 2004; Araya, Rojas, Fritsch, Gaete, Rojas, Simon & Peters 2003; Arthur, Jagger, Lindesay & Matthews 2002; Blanchard, Waterreus & Mann 1999; Brown, Shye, McFarland, Nichols, Mullooly & Johnson 2000; Bruce, Have, Reynolds, Katz, Schulberg, Mulsant et al. 2004; Capoccia, Boudreau, Blough, Ellsworth, Clark, Stevens et al. 2004; Ciechanowski, Wagner, Schmaling, Schwartz, Williams, Diehr et al. 2004; Finley, Rens, Pont, Gess, Louie, Bull et al. 2003; Fortney, Pyne, Edlund, Williams, Robinson, Mittal et al. 2007; Goldberg, Wagner, Fihn, Martin, Horowitz, Christensen et al. 1998; Hedrick, Chaney, Felker, Liu, Hasenberg, Heagerty et al. 2003; Hunkeler, Meresman, Hargreaves, Fireman, Berman, Kirsch et al. 2000; Jarjoura, Polen, Baum, Kropp, Hetrick & Rutecki 2004; Katon, Von Korff, Lin, Walker, Simon, Bush et al. 1995; Katon, Robinson, Von Korff, Lin, Bush, Ludman et al. 1996; Katon, Rutter, Ludman, Von Korff, Lin, Simon et al. 2001; Katon, Russo, Von Korff, Lin, Simon, Bush et al. 2002; Katzelnick, Simon, Pearson, Manning, Helstad, Henk et al. 2000; Lin, Simon, Katon, Russo, Von Korff, Bush et al. 1999; Lin, Von Korff, Russo, Katon, Simon, Unützer et al. 2000; Miranda, Chung, Green, Krupnick, Siddique, Revicki et al. 2003; Oslin, Sayers, Ross, Kane, Have, Conigliaro et al. 2003; Peveler, George, Kinmonth, Campbell & Thompson 1999; Pyne, Rost, Zhang, Williams, Smith & Fortney 2003; Rickles, Svarstad, Statz-Paynter, Taylor & Kobak 2005; Rollman, Hanusa, Lowe, Gilbert, Kapoor & Schulberg 2002; Rost, Nutting, Smith, Werner & Duan 2001; Sherbourne, Wells, Duan, Miranda, Unützer, Jaycox et al. 2001; Simon, Von Korff, Rutter & Wagner 2000; Simon, Ludman, Tutty, Operskalski & Von Korff 2004; Swindle, Rao, Helmy, Plue, Zhou, Eckert et al. 2003; Trivedi, Rush, Crismon, Kashner, Toprac, Carmody et al. 2004; Unützer, Rubenstein, Katon, Tang, Duan, Lagomasino et al. 2001; Unützer, Katon, Callahan, Williams, Hunkeler, Harpole et al. 2002; Worrall, Angel, Chaulk, Clarke & Robbins 1999), 3 cluster-randomised trials (Datto, Thompson, Horowitz, Disbot & Oslin 2003; Dietrich, Oxman, Williams, Schulberg, Bruce, Lee et al. 2004; Dobscha, Corson, Hickam, Perrin, Kraemer & Gerrity 2006), 1 case-control study (Flaherty, McBride, Marzouk, Miller, Chien, Hanchett et al. 1998), 1 controlled before-after study (Solberg, Fischer, Wei, Rush, Conboy, Davis et al. 2001), 1

Potentialy relevant reviews identified and title/abstract screened for retrieval: *n=201*

Reviews excluded: *n=151*

Reasons *(reviews may be excluded for more than one reason):*

I Focus on single-component interventions: n=93
II No systematic review or meta-analysis: n=96
III Main focus on other condition than depression: n=16
IV Main focus on other than adult population: n=15

Reviews retrieved for full text evaluation: *n=50*

Reviews excluded: *n=39*

Reasons *(reviews may be excluded for more than one reason):*

I Focus on single-component interventions: n=11
II No systematic review or meta-analysis: n=19
III Main focus on other condition than depression: n=2
IV Main focus on other than adult population: n=5

Systematic reviews included in the analysis: *n=11*

Empirical studies identified from included reviews and title/abstract screened for retrieval: *n=201*

Empirical studies excluded: *n=122*

Reasons *(studies may be excluded for more than one reason):*

I Study before 1995: n=3
II Single-component intervention: n=85
III Main focus on other condition than depression: n=56
IV Main focus on other than adult population: n=1
V Abstract not available: n=1

Empirical studies retrieved for full text evaluation: *n=79*

Empirical studies excluded: *n=33*

Reasons *(studies may be excluded for more than one reason):*

I Single-component intervention: n=7
II Main focus on other condition than depression: n=7
III No relevant outcome measure reported: n=21

Empirical studies included in the analysis: *n=46*

Figure 1   QUORUM study in- and exclusion flowchart (Moher et al. 1999)

longitudinal cohort observation (Aubert, Fulop, Xia, Thiel, Maldonato & Woo 2003), 1 naturalistic study with random allocation (Mann, Blizard, Murray, Smith, Botega, MacDonald et al. 1998), 1 quasi-experimental design (Cuijpers & van Lammeren 2001) and 1 randomised uncontrolled trial (Llewellyn-Jones, Baikie, Smithers, Cohen, Snowdon & Tennant 1999).

7.3.2 Findings from systematic reviews

The systematic reviews included in this review (Appendix Table 7S1) summarise evidence on a wide variety of chronic care management strategies for depression, such as guideline-based care, nurse-led interventions, mostly combined with patient education, collaborative care, community-based interventions and stepped care. Common aspect of the programmes is their strong focus on quality of care processes to improve the management and outcomes of depression, including self-management.

Variation in the inclusion criteria of reviews was found with respect to populations and settings. For example, while all studies concern depression, some reviews included a wide variety of depressive conditions (Neumeyer-Gromen, Lampert, Stark & Kallischnigg 2004; Williams, Gerrity, Holsinger, Dobscha, Gaynes & Dietrich 2007). Patients were managed in the primary care setting in 2 studies (Gilbody, Bower, Fletcher, Richards & Sutton 2006; Williams, Gerrity, Holsinger, Dobscha, Gaynes & Dietrich 2007), 2 reviews chose a community-based setting (Frederick, Steinman, Prohaska, Satariano, Bruce, Bryant et al. 2007; Gensichen, Beyer, Muth, Gerlach, Von Korff & Ormel 2006) and in the other reviews setting was not an inclusion criterion.

Also, reported outcome measures vary. Most, but not all, systematic reviews (n=7) report on depression severity (Badamgarav, Weingarten, Henning, Knight, Hasselblad, Gano et al. 2003; Gensichen, Beyer, Muth, Gerlach, Von Korff & Ormel 2006; Gilbody, Whitty, Grimshaw & Thomas 2003; Gilbody, Bower, Fletcher, Richards & Sutton 2006; Gilbody, Bower & Whitty 2006; Neumeyer-Gromen, Lampert, Stark & Kallischnigg 2004; Vergouwen, Bakker, Katon, Verheij & Koerselman 2003), 5 reviews report on adherence (Badamgarav, Weingarten, Henning, Knight, Hasselblad, Gano et al. 2003; Gensichen, Beyer, Muth, Gerlach, Von Korff & Ormel 2006; Neumeyer-Gromen, Lampert, Stark & Kallischnigg 2004; Vergouwen, Bakker, Katon, Verheij & Koerselman 2003; Williams, Gerrity, Holsinger, Dobscha, Gaynes & Dietrich 2007), 2 reviews report on patient compliance (Badamgarav, Weingarten, Henning, Knight, Hasselblad, Gano et al. 2003; Gilbody, Bower, Fletcher, Richards & Sutton 2006), 3 reviews report symptom improvement or remission (Christensen, Griffiths, Gulliver, Clack, Kljakovic & Wells 2008; Gensichen, Beyer, Muth, Gerlach, Von Korff & Ormel 2006; Williams, Gerrity, Holsinger, Dobscha, Gaynes & Dietrich 2007), 2 reviews report on health-related quality of life (Gilbody, Whitty, Grimshaw & Thomas 2003; Neumeyer-Gromen,

Lampert, Stark & Kallischnigg 2004) and 1 review report an expert rating of effectiveness (Frederick, Steinman, Prohaska, Satariano, Bruce, Bryant et al. 2007). Two studies were full economic evaluations (Gilbody, Bower & Whitty 2006; Pirraglia, Rosen, Hermann, Olchanski & Neumann 2004).

Overall, the reviews draw positive conclusions about the effectiveness of chronic care programmes for depression. All reviews that report on depression severity or treatment response show positive results. The results on costs are less convincing, since 1 of the 2 economic evaluations found increased costs compared to usual care (Gilbody, Bower & Whitty 2006). It remains unclear which specific interventions or components are most effective (Gilbody, Whitty, Grimshaw & Thomas 2003; Williams, Gerrity, Holsinger, Dobscha, Gaynes & Dietrich 2007).

7.3.3   Findings from primary studies

Of the 46 primary studies, 61% (n=28) scored good and 39% (n=18) scored moderate on methodological quality (Appendix Table 7S2). Twenty-two of the 46 studies (48%) reported a follow-up of 12 months or longer. Most of the studies (83%; n=38) were performed in the USA.

The most frequently included component concerned DSD (89%; n=41), followed by CIS (78%; n=36), DS (76%; n=35) and SMS (74%; n=34). Thirteen studies (28%) evaluated a programme with 2 components, 12 with 3 components (26%) and 21 with 4 components (46%). Five of the 13 programmes with 2 components included the combination of SMS and DSD. Other combinations were of CIS and DS (n=3), DSD and CIS (n=2), DSD and DS (n=2) and SMS and CIS (n=1). The most common combination of 3 components was DSD, CIS and DS (n=6). All studies with 3 components included DS.

The extent to which the chronic care management components are applied varied between studies. SMS frequently consisted of patient education and self-management tools, aiming at encouraging treatment compliance. DSD was often performed by introduction of a specialised clinician, nurse and/or case manager added to the multidisciplinary care team or involving primary care, concerning routine follow-up or telephone counselling, stepped care or collaborative care management. CIS mainly consisted of monitoring of symptoms or clinical status and treatment adherence or outcomes, as well as providing feedback or recommendations for further management by care professionals or patients. DS concerned in particularly (locally adapted) evidence-based guidelines or clinical algorithms, personalised treatment recommendations, consultation or training by a mental healthcare professional.

Outcome measures mostly assessed in primary studies are depression severity (91%; n=42), quality of life (50%; n=23), treatment response (48%; n=22) and remission (26%; n=12). Data on processes of care were also collected in the 46

studies: treatment compliance (43%; n=20), guideline adherence (41%; n=19), healthcare consumption (22%; n=10) and costs (20%; n=9).

Depression severity was reported in most studies, but measured with 12 different instruments. The most frequently used instrument, in 16 studies (Aubert, Fulop, Xia, Thiel, Maldonato & Woo 2003; Capoccia, Boudreau, Blough, Ellsworth, Clark, Stevens et al. 2004; Ciechanowski, Wagner, Schmaling, Schwartz, Williams, Diehr et al. 2004; Dietrich, Oxman, Williams, Schulberg, Bruce, Lee et al. 2004; Dobscha, Corson, Hickam, Perrin, Kraemer & Gerrity 2006; Goldberg, Wagner, Fihn, Martin, Horowitz, Christensen et al. 1998; Hedrick, Chaney, Felker, Liu, Hasenberg, Heagerty et al. 2003; Katon, Von Korff, Lin, Walker, Simon, Bush et al. 1995; Katon, Robinson, Von Korff, Lin, Bush, Ludman et al. 1996; Katon, Rutter, Ludman, Von Korff, Lin, Simon et al. 2001; Katon, Russo, Von Korff, Lin, Simon, Bush et al. 2002; Simon, Von Korff, Rutter & Wagner 2000), is the 20 items version of the Hopkins Symptom Checklist (HSCL-20) (Walker, Sharpe, Kroenke & Murray 2010). The HSCL-20 mean scores range from 0.68 to 1.63 on a scale of 0-4 in the experimental groups, showing mainly improvement as compared to the control groups (a score of <0.50 is considered depression free) (Vannoy, Arean & Unützer 2010). However, these findings could not be pooled as only 4 studies (Ciechanowski, Wagner, Schmaling, Schwartz, Williams, Diehr et al. 2004; Dietrich, Oxman, Williams, Schulberg, Bruce, Lee et al. 2004; Hedrick, Chaney, Felker, Liu, Hasenberg, Heagerty et al. 2003; Katon, Von Korff, Lin, Walker, Simon, Bush et al. 1995) reported the results completely, while missing data could not be estimated, nor retrieved from the authors. Depression severity measured with other instruments did also not reach a sufficient number of studies for pooling.

Health-related quality of life was mostly assessed with the Medical Outcomes Study short form (MOS SF; n=21). The 12-item and 36-item version (MOS SF-12 and MOS SF-36) were most frequently used (n=8 and n=11 respectively). But data were often reported incompletely, could not be estimated, nor retrieved from the authors and, as a result, could not be pooled. The mental health scales in both SF-12 and SF-36 can be aggregated in a comparable manner into a summary measure, the Mental Component Summary (MCS) score (Farivar, Cunningham & Hays 2007). Eight studies reported the MCS (Aubert, Fulop, Xia, Thiel, Maldonato & Woo 2003; Capoccia, Boudreau, Blough, Ellsworth, Clark, Stevens et al. 2004; Dobscha, Corson, Hickam, Perrin, Kraemer & Gerrity 2006; Fortney, Pyne, Edlund, Williams, Robinson, Mittal et al. 2007; Hedrick, Chaney, Felker, Liu, Hasenberg, Heagerty et al. 2003; Hunkeler, Meresman, Hargreaves, Fireman, Berman, Kirsch et al. 2000; Sherbourne, Wells, Duan, Miranda, Unützer, Jaycox et al. 2001; Trivedi, Rush, Crismon, Kashner, Toprac, Carmody et al. 2004) and 2 studies reported significant improvement on quality of life in the chronic care management condition for MCS (Aubert, Fulop, Xia, Thiel, Maldonato, Woo 2003; Fortney, Pyne, Edlund, Williams, Robinson, Mittal et al. 2007). However, data on the MCS were incomplete and the studies could not be pooled.

For the other frequently reported outcome measures, treatment response, we performed a meta-analysis and meta-regression analyses. To be able to perform a meta-analysis and meta-regression-analyses for the most frequently reported process measures, treatment compliance and guideline adherence, we constructed a process measure called treatment adherence.

Study of subgroup	Risk ratio M-H, Random, 95% CI	Risk ratio M-H, Random, 95% CI
Araya 2003	2.50 [1.86, 3.36]	
Brown 2000 AD	0.74 [0.55, 1.00]	
Bruce 2004	1.24 [1.00, 1.53]	
Ciechanowski 2004	2.89 [1.49, 5.59]	
Dietrich 2004	1.29 [1.04, 1.59]	
Finley 2003	0.75 [0.46, 1.23]	
Fortney 2007	1.35 [0.98, 1.85]	
Hendrick 2003	1.20 [0.74, 1.97]	
Katon 1995	1.14 [0.92, 1.40]	
Katzelnick 2000	1.62 [1.27, 2.08]	
Oslin 2003	2.11 [1.05, 4.22]	
Rickles 2005	1.14 [0.82, 1.59]	
SImon 2004 TCM	1.18 [0.95, 1.48]	
Simon 2004 TCM+	1.35 [1.09, 1.66]	
Unutzer 2002	2.33 [2.00, 2.72]	
Total (95%) CI	**1.38 [1.15, 1.67]**	

Favours control   Favours experiment

Total events
Heterogeneity: Tau2 = 0.11; Chi2 = 97.67, df = 14 (P < 0.00001); I² = 86%
Test for overal affect: Z = 3.38 (P = 0.0007)

Figure 2   **Meta-analysis of treatment adherence. Forest plot of comparison**

7.3.4 Meta-analysis on treatment response

Differences in the operationalisation of treatment response allow for meta-analysis when we define treatment response as the absolute number of patients with at least 50% improvement in depression symptoms. Of the 22 studies that reported treatment response, seven studies reported incomplete data that could not be estimated nor retrieved from the authors and were therefore excluded for the meta-analysis. The pooled relative risk (Araya, Rojas, Fritsch, Gaete, Rojas, Simon,

Peters 2003; Brown, Shye, McFarland, Nichols, Mullooly & Johnson 2000; Bruce, Have, Reynolds, Katz, Schulberg, Mulsant et al. 2004; Ciechanowski, Wagner, Schmaling, Schwartz, Williams, Diehr et al. 2004; Dietrich, Oxman, Williams, Schulberg, Bruce, Lee et al. 2004; Finley, Rens, Pont, Gess, Louie, Bull et al. 2003; Fortney, Pyne, Edlund, Williams, Robinson, Mittal et al. 2007; Hedrick, Chaney, Felker, Liu, Hasenberg, Heagerty et al. 2003; Katon, Von Korff, Lin, Walker, Simon, Bush et al. 1995; Katzelnick, Simon, Pearson, Manning, Helstad, Henk et al. 2000; Oslin, Sayers, Ross, Kane, Have, Conigliaro et al. 2003; Rickles, Svarstad, Statz-Paynter, Taylor & Kobak 2005; Simon, Ludman, Tutty, Operskalski & Von Korff 2004; Unützer, Katon, Callahan, Williams, Hunkeler, Harpole et al. 2002) for treatment response with chronic care management compared to the control intervention (mostly usual care) is 1.38 (95% CI: 1.15-1.67; Figure 2; Table 1). However, statistical heterogeneity was apparent (I^2=86%).

Subgroup analyses for study quality showed significant improvements (RR = 1.39; 95% CI: 1.12-1.73) for good study quality, but also high heterogeneity (I^2=88%), whereas moderate quality studies did not show significant effect. Significant improvements were shown by subgroup analyses in studies with follow-up within 12 months (RR=1.31; 95% CI: 1.09-1.58) as well as in studies with follow-up at 12 months or later (RR=1.50; 95% CI: 1.04-2.15), both with high heterogeneity (respectively I^2=72% and I^2=91%). In subgroup analyses, no effect could be reported for studies with 2 or 3 programme components, while studies with 4 components showed significant improvements (RR = 1.42; 95% CI: 1.14-1.77) and high heterogeneity (I^2=87%).

Subgroup analyses on patient characteristics revealed a significant effect of chronic care management in major depressive disorder (RR=1.38; 95% CI: 1.14-1.67; I^2=85%), while not in minor depressive disorder. In all other subgroups of patients with specific characteristics that were explored using meta-analyses, a significant effect of chronic care management was found: in all ages group (RR=1.25; 95% CI: 1.04-1.49; I^2=76%), as well as in patients 60 years or older (RR=1.94; 95% CI: 1.15-3.28; I^2=92%); in Veterans (RR=1.39; 95% CI: 1.08-1.78; I^2=0%), as well as in Non-Veterans (RR=1.37; 95% CI: 1.11-1.70; I^2=89%) and in patients with a new current episode of major depressive disorder (OR=2.02; 95% CI: 1.78-2.30; I^2=90%) as well as in patients with a recurrent episode (OR=1.82; 95% CI: 1.44-2.30; I^2=65%).

7.3.5 Meta-regression analyses on treatment response

Results of the meta-regression analyses on treatment response are shown in Table 1. In the meta-regression analyses, study quality explained 36.6% of the variance (p=0.0352), which is in line with the subgroup analyses. Meta-regression analyses showed no significance for length of follow-up on the relative risk of treatment response or for a number of components on the relative risk of treatment response,

Study of subgroup	Risk ratio M-H, Random, 95% CI	Risk ratio M-H, Random, 95% CI
Hedrick 2003	1.03 [0.85, 1.24]	
Katon 1995 minor	1.98 [1.44, 2.72]	
Katon 1996	1.40 [1.05, 1.86]	
Katon 2002 high severity	1.88 [1.15, 3.05]	
Lin 1999	1.20 [0.93, 1.55]	
Peveler 1999	1.66 [1.10, 2.51]	
SImon 2004 TCM	1.31 [1.06, 1.63]	
Simon 2004 TCM+	1.22 [0.97, 1.52]	
Total (95%) CI	1.36 [1.16, 1.58]	

0.1   0.2   0.5   1   2   5   10
Favours control   *Favours experiment*

Total events
Heterogeneity: Tau2 = 0.03; Chi2 = 17.52, df = 7 (P = 0.01); I^2 = 60%
Test for overal affect: Z = 3.91 (P < 0.0001)

Figure 3   Meta-analysis of treatment adherence. Forest plot of comparison

which implies that these variables could not significantly explain the heterogeneity between studies. Meta-regression analyses showed no significant effects on treatment response for any of the patient characteristics subgroups.

7.3.6 Meta-analysis on treatment adherence

A variety of outcome measures was used for assessing either patient compliance (in 20 studies) or adherence by the care professional (in 19 studies), such as percentage of patients following clinician's treatment recommendations, percentage of patients reporting to take the full dosage of antidepressants during ≥80% of days, percentage of patients receiving treatment recommendations for depression, percentage of patients receiving prescription for antidepressants or percentage of patients with appropriate medication. However, data could not be pooled for both measures because of incomplete data, always leaving less than 8 studies. Therefore, we constructed a process measure called treatment adherence, which was defined as the combination of patient compliance and adherence by the care professional conform guidelines: the percentage of patients using an adequate dosage of an adequate antidepressant (AD) for at least 90 days, measured as either patients complying to evidence-based medication treatment policies, or care professionals adhering to evidence-based practice guidelines. For 11 primary studies, this measure could be constructed, but for 3 studies incomplete data could not be estimated or retrieved from the authors, with 8 primary studies remaining for data pooling (Hedrick, Chaney, Felker, Liu, Hasenberg, Heagerty et al. 2003;

	No. of studies	No. of participants	Relative risk # (95%-CI; I²)	Explained heterogeneity (P-value)
Treatment response,	15	5935	1.38 (1.15-1.67; 86%)*	36.6% (0.0352)*
Study quality				
Poor	0	0	Not estimable	
Moderate	3	620	1.26 (0.95-1.67; 31%)	
Good	12	5315	1.39 (1.12-1.73; 88%)*	
Length of follow-up				3.8% (0.5297)
<1 year	9	2002	1.31 (1.09-1.58; 72%)*	
≥1 year	6	3933	1.50 (1.04-2.15; 91%)*	
Number of components				13.8% (0.3731)
2	2	1005	1.19 (0.43-3.31; 87%)	
3	3	592	1.42 (0.97-2.09; 71%)	
4	10	4338	1.42 (1.14-1.77; 87%)*	
Patient characteristics				
Minor vs. major depressive disorder				13.4% (0.0845)
Minor depression	2	253	1.54 (0.44-5.46; 92%)	
Major depression	14	5682	1.38 (1.14-1.67; 85%)	
Age group				22.8% (0.0605)
All ages	12	3265	1.25 (1.04-1.49; 76%)*	
60 years or older	3	2290	1.94 (1.15-3.28; 92%)*	
Veterans vs. non-veterans				0% (0.8393)*
Veterans	3	1738	1.39 (1.08-1.78; 0%)*	
Non-veterans	12	5197	1.37 (1.11-1.70; 89%)*	
New current episode vs. recurrent episode				2.7% (0.3205)
New current episode	10	4576	2.02 (1.78-2.30; 90%)#*	
Recurrent episode	6	1359	1.82 (1.44-2.30; 65%)#*	

*CI: confidence interval; I² statistical heterogeneity; # if marked an odds ratio in a fixed model was used; * p-value <0.05*

Table 1   Results of the meta-analysis and meta-regression analyses of treatment

Katon, Von Korff, Lin, Walker, Simon, Bush et al. 1995; Katon, Robinson, Von Korff, Lin, Bush, Ludman et al. 1996; Katon, Russo, Von Korff, Lin, Simon, Bush et al. 2002; Lin, Simon, Katon, Russo, Von Korff, Bush et al. 1999; Peveler, George, Kinmonth, Campbell & Thompson 1999; Simon, Ludman, Tutty, Operskalski & Von Korff 2004 (Figure 3; Table 2).

Overall, the risk ratio of chronic care management is 1.36 in a random effect model (95% CI: 1.16–1.58; I²=60%). Subgroup analyses showed that good quality studies did reach a significant improvement in treatment adherence (RR=1.32; 95% CI: 1.16–1.50) and low heterogeneity (I²=7%), while studies of moderate quality did not show a significant effect. Studies with 4 programme components, with apparent heterogeneity (I²=62%), showed significant effects (RR=1.33; 95% CI: 1.13–1.57) and so did the 1 study with 2 components (RR=1.66; 95% CI: 1.10-2.51; p=0.02). Subgroup analyses showed a significant effect of studies with a length of follow-

up within 1 year (RR=1.35; 95% CI: 1.13–1.62; I^2=66%), while studies reporting longer-term (≥1 year) did not show significant effect.

Subgroup analyses on patient characteristics revealed that the effect of chronic care management in major depressive disorder was additionally significant (RR=1.24; 95% CI: 1.09-1.41; I^2=36%), but less strong than in minor depressive disorder (RR=1.88; 95% CI: 1.46-2.42; I^2=0%). All age groups were included in all studies, so analysis on subpopulations of age groups could not be performed. In Non-Veterans, a significant effect was shown (RR=1.42; 95% CI: 1.23-1.63; I^2=39%); in Veterans (RR=1.03; 95% CI: 0.85-1.24) meta-analysis was not applicable, with only 1 study available. In patients with a new current episode of major depressive disorder, a significant effect was shown (OR=1.73; 95% CI: 1.36-2.20; I^2=0%), but not in patients with a recurrent episode (RR=1.49; 95% CI: 0.93-2.38; I^2=87%). This last group includes 2 studies on minor depression.

	No. of studies	No. of participants	Relative risk # (95%-CI; I^2)	Explained heterogeneity (P-value)
Treatment response,	8	1563	1.36 (1.16-1.58; 60%)*	
Study quality				1.4% (0.9137)
Poor	0	0	Not estimable	
Moderate	3	529	1.39 (0.95-2.04; 85%)	
Good	5	1034	1.32 (1.16-1.50; 7%)*	
Length of follow-up				25.1% (0.2691)
<1 year	6	1379	1.35 (1.13-1.62; 66%)*	
≥1 year	2	184	1.43 (0.92-2.22; 63%)	
Number of components				18.3% (0.3765)
2	1	108	1.66 (1.10-2.51; NA)	
3	0	0	Not estimable	
4	7	1455	1.33 (1.13-1.57; 62%)*	
Patient characteristics				
Minor vs. major depressive disorder				88.7% (0.0083)
Minor depression	2	214	1.88 (1.46-2.42; 0%)*	
Major depression	7	1349	1.24 (1.09-1.41; 36%)*	
Veterans vs. non-veterans				Not estimable
Veterans	1	250	1.03 (0.85-1.24; NA)	
Non-veterans	7	1313	1.42 (1.23-1.63; 39%)*	
New current episode vs. recurrent episode				9.4% (0.9419)*
New current episode	3	464	1.73 (1.36-2.20; 0%)#*	
Recurrent episode	6	1099	1.49 (0.93-2.38; 87%)	

*CI: confidence interval; I^2 statistical heterogeneity; # if marked an odds ratio in a fixed model was used; * p-value <0.05. The variance between groups increased after adjustment, meaning that the variables in the meta-regression analysis cannot explain the differences between groups.*

Table 2 Results of the meta-analysis and meta-regression analyses of treatment adherence

7.3.7 Meta-regression analyses on treatment adherence

Results of the meta-regression analysis on treatment response are shown in Table 2. Although subgroup analyses showed that good quality studies, studies with 4 programme components and studies with a length of follow-up of 1 year or less showed significant improvement in treatment adherence in intervention groups as compared to control groups, meta-regression analyses showed no significance for number of components, study quality or length of follow-up on the risk ratio of treatment adherence.

However, meta-regression analysis showed significant effects in patients with major depression, explaining 88.7% (p=0.0083) of the variance between studies in effectiveness. Meta-regression analysis did not show significance for recurrence of depressive episodes on the odds ratio of treatment response, which implies that this variable could not significantly explain the heterogeneity between studies. Meta-regression analyses with age groups or Veterans could not be performed.

7.4 Discussion

7.4.1 Findings from this study

We summarised previous reviews and found mainly positive effects of chronic care management on depression outcomes and processes: depression severity significantly reduced, while quality of life, treatment adherence and treatment response significantly improved. Our new and expanded meta-analyses also showed positive effects of chronic care management on treatment response as well as on treatment adherence in intervention groups as compared to control groups. We hypothesised that differences in outcomes between studies can be explained by differences in methodological study quality, length of follow-up, number of included intervention components according to the CCM, or patient characteristics. Meta-regression analyses confirmed several associations found in our subgroup analyses. Diversity in methodological quality of the study explained 36.6% of present heterogeneity in treatment response. This implies that more good quality studies are needed in order to demonstrate the potential of chronic disease management for depression. Depression severity in the study population did not significantly explain the non-random variation in treatment response. Depression severity, however, did explain 88.7% of present heterogeneity in treatment adherence.

This implies that chronic care management, in order to reach its full potential, needs to be tailored to the depression severity level of patients. Diversity in length of follow-up or number of programme components did not explain heterogeneity in treatment response or in treatment adherence.

The method of meta-regression analysis in identifying active ingredients in multi-component interventions has been recommended by Bower et al. (Bower, Gilbody, Richards, Fletcher & Sutton 2006). In addition to previous studies, our systematic review gives a comprehensive overview of previous reviews and includes meta-analyses as well as the first meta-regression analyses that attempt to explain the heterogeneity in outcomes of chronic care management programmes for depression by analysing differences in study quality, length of follow-up, number of CCM components and patient characteristics.

7.4.2 Assumed sources of heterogeneity

The use of quality scales in systematic reviews has been criticised, particularly as a means to exclude poor quality trials from analyses or to incorporate information on study quality as weighting factors in analyses. We studied study quality as a covariate in the meta-regression, since inclusion of good and poor quality trials in a systematic review may increase heterogeneity of estimated effects across trials (Jüni, Witschi, Bloch & Egger 1999; Jüni, Altman, Egger 2001; Gellatly, Bower, Hennessy, Richards, Gilbody & Lovell 2007; Jané-Llopis, Hosman, Jenkins & Anderson 2003). In our study, subgroup analyses indeed showed that good study quality explained present heterogeneity for treatment response, as well as for treatment adherence. Our meta-regression analysis did confirm the association with treatment response.

Length of follow-up is important to complex multi-component interventions, such as chronic care management, because the required behavioural, organisational and cultural changes need time to come about (Coleman, Austin, Brach & Wagner 2009). Hence, studies with a short follow-up period may either over- or underestimate effects (Linden & Adler-Milstein 2008). On treatment adherence, our subgroup analyses showed that a length of follow-up of 1 year or less showed significant improvement in intervention groups as compared to control groups, whereas a longer follow-up did not. Apparently, the effect of chronic care management on treatment adherence is not sustainable over a longer period of time, which could be explained by the need for continuous effort in depression management in order to achieve sustained improvement, which is shown in previous reviews (Katon & Guico-Pabia 2011; Gilbody, Bower, Fletcher, Richards & Sutton 2006; Jané-Llopis, Hosman, Jenkins & Anderson 2003; Paykel 2007). However, our meta-regression analysis did not confirm this.

The number of components included in an intervention was investigated as a potential cause of heterogeneity in results, since the CCM assumes that more comprehensive programmes will attain more promising results (Wagner, Austin, Davis, Hindmarsh, Schaefer & Bonomi 2001; Wagner 1998; Jané-Llopis, Hosman, Jenkins & Anderson 2003; Wagner, Bennett, Austin, Greene, Schaefer & Von Korff 2005). In our subgroup analyses, programmes with 4 components showed

significant effects on treatment response and treatment adherence, whereas programmes with 2 and 3 components did not. This implies that a combination of components is needed to improve chronic care management. This was also found in earlier reviews (Coleman, Austin, Brach & Wagner 2009; Bower, Gilbody, Richards, Fletcher & Sutton 2006; Gilbody, Whitty, Grimshaw & Thomas 2003; Aubert, Fulop, Xia, Thiel, Maldonato & Woo 2003).

Variation in the inclusion criteria of previous reviews was found with respect to populations and settings and therefore patient characteristics are expected to be a potential cause of heterogeneity. The heterogeneity of the depression syndrome in itself has been discussed as an underlying reason for lacking clinically relevant effects of treatments (Østergaard, Jensen & Bech 2011). Meanwhile, the disease severity of the target population is expected to be related to the optimal intensity of specific interventions (Mattke, Seid & Ma 2007; Gellatly, Bower, Hennessy, Richards, Gilbody & Lovell 2007). However, the optimal relation between disease severity and the variation within the chronic care management elements is not yet known. For patients to benefit the most from specific interventions, how can these interventions within a depression management programme be stepped in intensity, while symptom monitoring ensures that patients step up timely to more intensive treatments when needed, in such a way that satisfying outcomes will be achieved? For instance, it is of interest to identify when a case manager should be preferred above other programme components and vice versa (Gensichen, Beyer, Muth, Gerlach, Von Korff & Ormel 2006).

In our subgroup analyses, patient characteristics revealed significant effects of chronic care management in all subgroups, except in treatment response for patients with minor depression and in treatment adherence for patients with a recurrent episode. This finding implies that taking account of depression severity, by improving treatment adherence, contributes to maximising the effectiveness of chronic care management for depression, which is in accordance with previous reviews that found that stepped-care approaches need to be defined by future research (Williams, Gerrity, Holsinger, Dobscha, Gaynes & Dietrich 2007; Bower & Gilbody 2005).

7.4.3 Limitations of this study

Our study used an extensive search strategy following the internationally accepted definition of chronic care management (Singh 2008). Nevertheless, some limitations should be noted. First, it is disputable whether the HTA-DM instrument (Steuten, Vrijhoef, Merode, Severens & Spreeuwenberg 2004), the only relevant and tested instrument for assessing the quality of chronic care management, allows for proper scoring of items that biases the effect of interventions for depression, as it focuses primarily on the quality of reporting. Further validation of a quality instrument for studies evaluating complex interventions, such as chronic care programmes, is needed.

Our analyses of heterogeneity were limited by the quality and comprehensiveness of the describing of interventions by primary studies. Operationalisations of the intervention components are, in particular, scarcely reported and the care received by intervention as well as control patients is often poorly described, which complicates the mapping of intervention components to the CCM and makes comparisons between studies difficult. Many studies exhibit a paucity of descriptive detail in reporting data, which necessitates either the use of estimates, or exclusion from data analyses. Standard deviations and p-values are rarely reported, for example, several studies reported only mean score differences or the percentage with a difference in scores, actual values for the intervention group or one of the study arms only or fractions of patients accomplishing treatment response, odds ratio's or figures, rather than the actual values.

Meanwhile, a great variety of sometimes difficult to compare instruments is used to measure outcomes such as patient satisfaction or quality of life, which complicates comparing or pooling of data. For example, less than 50% of studies that assessed quality of life by means of the SF-12 or SF-36, chose to measure the same scales or components of these instruments and studies were thus incomparable. Moreover, the outcomes of our review are restricted to those effect measures used most frequently in the existing evidence on chronic care management for depression, whereas others, such as patient compliance or adherence by the care professional to other interventions than pharmacotherapy or patients' satisfaction with care, may be equally or even more important. Despite the premises of control of cost by chronic care programmes, most studies lack information on healthcare costs. While Pirraglia et al. (Pirraglia, Rosen, Hermann, Olchanski & Neumann 2004) found lower costs for chronic care management, Gilbody et al. (Gilbody, Bower & Whitty 2006) found that chronic care management resulted in better outcomes, but increased costs compared to usual care and further research is needed to assess the cost-effectiveness.

Also, as was noticed by Bower et al. (Bower, Gilbody, Richards, Fletcher & Sutton 2006), in meta-analysis, active ingredients that are necessary in establishing effectiveness but are not varying between programmes, will not be revealed. Although the potential causes of heterogeneity included in our analyses were selected on the basis of the available evidence, variation in effect sizes across trials of chronic care management for depression may be caused by other study-level factors, such as differences in study design, other characteristics of the target population and implementation context. In addition, the degree of integration between the components that constitute a specific chronic care programme may also be an important cause of statistical heterogeneity. Our approach of mapping interventions to the CCM did not take this factor into account, while a programme in which various elements are strongly interrelated, as is prescribed by the CCM (Wagner, Austin, Davis, Hindmarsh, Schaefer & Bonomi 2001; Wagner 1998), is likely to result in better outcomes than a programme in which elements are more loosely coupled or not integrated in any sense.

7.4.4 Recommendations for future research

As our insight into the effects of disease management for depression as a chronic condition is limited, a wide range of scientific methodologies should be embraced, providing appropriate and effective methods for addressing the crucial pragmatic questions about improvement: what is it about the mechanism of an intervention or programme that works, for whom and under what circumstances (Davidoff, Batalden, Stevens, Ogrinc & Mooney 2009)? Since the heterogeneity in treatment response can be explained partly by study quality, we emphasise the importance of good quality studies. Also, research on other possible sources of hetereogeneity than we explored in this study, is needed.

Chronic care management is based on the presumption that tackling the burden of chronic disease requires evidence-based changes of both patients and professionals, in behaviour, culture and communication (Lemmens, Nieboer, van Schayck, Asin & Huijsman 2008; Linden, Adams & Roberts 2003). Few trials, however, measure intermediary factors, such as patients' knowledge of their disease or their self-management skills, that must be positively influenced before an improvement in clinical measures can occur (Lemmens, Nieboer, van Schayck, Asin & Huijsman 2008). Although the context or the degree to which programme components are implemented are expected to influence the effectiveness of chronic care management, as implementing such complex interventions is essentially a process of social change (Wagner, Bennett, Austin, Greene, Schaefer & Von Korff 2005; Berwick 2008), studies reveal little about these influences. Measuring such person-centred variables should become standard procedure in order to gain insight into the working mechanisms of chronic care management programmes as well as for decisions to be made on optimal treatment policies and the design of depression care. Since heterogeneity in treatment adherence can be explained partly by severity of the depression, more research on how to take account of depression severity in chronic care management strategies for depression is needed.

Chapter 8

The cost-utility of stepped-care algorithms according to depression guideline recommendations – results of a state-transition model analysis

Summary

Background. Evidence-based clinical guidelines for major depressive disorder (MDD) recommend stepped-care strategies for sequencing evidence-based treatments conditional on treatment outcomes. This study aims to evaluate the cost-effectiveness of stepped care as recommended by the multidisciplinary clinical guideline vis-à-vis usual care in the Netherlands.

Methods. Guideline-congruent care as described in stepped-care algorithms for either mild MDD or moderate and severe MDD was compared with usual care in a health-economic state-transition simulation model. Incremental costs per QALY gained were estimated over five years from a healthcare perspective.

Results. For mild MDD, the cost-utility analysis showed a 67% likelihood of better health outcomes against lower costs, and 33% likelihood of better outcomes against higher costs, implying dominance of guideline-congruent stepped care. For moderate and severe MDD, the cost-utility analysis indicated a 67% likelihood of health gains at higher costs following the stepped-care approach and 33% likelihood of health gains at lower costs, with a mean ICER of about € 3,200 per QALY gained. At a willingness to pay threshold of € 20,000 per QALY, the stepped-care algorithms for both mild MDD and moderate or severe MDD is deemed cost-effective compared to usual care with a greater than 95% probability.

Limitations. The findings of our decision-analytic modelling are limited by the accuracy and availability of the underlying evidence. This hampers taking into account all individual differences relevant to optimise treatment to individual needs.

Conclusions. It is highly likely that guideline-congruent stepped care for MDD is cost-effective compared to usual care. Our findings support current guideline recommendations.

"The future is independent of the past given the present."
Andrej Markov (1856-1922), c. 1913

8.1 Introduction

Major Depressive Disorder (MDD) diminishes quality of life and is associated with functional impairment, which has a tremendous impact on individuals, their relatives and society. In view of its high prevalence, MDD is costly from both a healthcare and a societal perspective (Ferrari et al. 2013; Chisholm et al. 2016).

Stepped-care service delivery can support decision making on gradually intensifying care according to patient's needs, while maximising the overall benefit of resources. Interventions that are lower in intensity are preferred in treatment choices if adequate and acceptable, to avert over-treatment. The course of symptoms and change of need steers treatment through monitoring of treatment response and periodically evaluating care, to avert under-treatment. Controlled studies have demonstrated the clinical effectiveness of stepped care in general medicine and mental health and addiction care (Bower & Gilbody 2005; Haaga 2000). Clinical guidelines for depression recommend stepped-care strategies that sequence evidence-based treatment options and monitor outcomes (Spijker et al. 2013; Meeuwissen et al. 2008; NICE 2018; Richards et al. 2012; NZGG 2008). This allows tailoring treatment intensity to the patient's needs while accounting for treatment response (or the lack thereof) in previous and less intensive treatment steps. Studies on the clinical effectiveness of stepped care in depressed patients found small positive effects on depression outcomes (van Straten et al. 2015; Firth et al. 2015). Other effectiveness studies for sequenced treatment strategies have shown positive results as well (van Dijk et al. 2015; Oosterbaan et al. 2013; van Orden et al. 2009; Trivedi et al. 2004). These studies showed that stepped-care interventions for depression are at least as effective as usual care, although current evidence is limited through methodological variety across studies. Although the evidence-base for the clinical effectiveness of stepped care for treating depression is growing, the evidence on cost-effectiveness of stepped care compared to care as usual is still limited (van Straten et al. 2015; Firth et al. 2015).

Insight into the cost-effectiveness of stepped care can help to optimise treatment allocation and improve the quality of care for depression in a cost-effective manner. This study employed a modelling approach to gain insight into the cost-effectiveness of stepped care, as suggested by Bower & Gilbody (2005). The aim of this study is to evaluate the cost-utility of depression care when applying stepped-care algorithms according to the Dutch Multidisciplinary Guideline for Depression (Spijker et al. 2013) in comparison to care as usual. This evidence-based guideline aims to reduce under-treatment as well as over-treatment and may therefore introduce health economic benefits that differ from usual care. Our hypothesis is that in stepped care health gains can be achieved cost-effectively, through either better outcomes or similar outcomes at reduced costs in the long run.

8.2 Methods

8.2.1 State-transition modelling approach

In this economic evaluation we have combined available evidence on clinical effectiveness and costs from different sources in a state-transition model. We used epidemiologic and clinical research data to take into account actual prevalences and severities to construct a representative clinical sample. We used clinical data to specify the percentage of each clinical subgroup that receives treatment and also the percentage that responds to treatment in each subgroup. Expert opinion was used to allocate patients to treatment. Next, we used effect sizes from meta-analyses to calculate how much improvement each clinical subgroup experiences from each type of treatment. Transitions across health states were modelled to assess the cost-utility (i.e. the healthcare costs per quality adjusted life year, QALY, gained) of guideline-based stepped-care scenarios for MDD compared to reference scenarios reflecting usual care.

8.2.2 Target population

The target population consists of adult patients in Dutch mental health care with mild, moderate or severe MDD without psychotic symptoms. In the Dutch population aged 18-64 years, 5.2% met the DSM-IV criteria for MDD in the last year, while the lifetime prevalence is 18.7% (de Graaf et al. 2010). This prevalence rate is comparable to other Western-European countries (Kessler et al. 2007).

8.2.3 Guideline-congruent care

The Dutch Multidisciplinary Guideline for Depression (Third revision; Spijker et

al. 2013) has been updated following the method of evidence-based guideline development, involving a large number of professional associations and patient participation. The developing and updating procedures are comparable to the methods and procedures of the National Institute for Health and Care Excellence (NICE 2014; Philips et al. 2004). For the current clinical guideline, stepped-care algorithms were developed to support care professionals with sequential treatment allocation that takes into account the severity, course and duration of symptoms. There are basic interventions to be offered to all patients in both algorithms. These are psycho-education, active monitoring of symptoms and structuring of the day. Minimal interventions, including bibliotherapy or (online) self-management, may be added when the patient prefers to. According to the guideline, based on the diagnosis of either mild or moderate to severe MDD and the recognition of a recurrent episode, following the stepped-care algorithm for either mild MDD or moderate and severe MDD is indicated (See Figures 1 and 2).

8.2.4 Comparator: care as usual

Care as usual (CAU) consists of all commonly available treatments in the healthcare system, often delivered in a mix of care. Guideline-congruent care is different from CAU in two ways: (a) basic interventions (i.e. psycho-education, active monitoring of symptoms, structuring of the day) are provided to all patients; and (b) the specific sequence and duration of evidence-based treatment interventions is made explicit. Treatment decisions are guided by observed treatment response such that patients who show no improvement at a certain time point are offered a next treatment step, often consisting of more intensive treatment.

8.2.5 Stepped-care scenarios and reference scenarios

We constructed two guideline-congruent stepped-care scenarios based on the algorithms in the Dutch Multidisciplinary Guideline for Depression, one for mild MDD, and another for moderate and severe MDD, as well as their CAU-reference scenarios. The number of patients reached per intervention, initially or after stepping up for patients who needed this (since insufficient effect was reached with previous treatment for any reason), was based on expert opinion of members of the Guideline Development Group, informed by literature review. Effect sizes of the interventions in guideline-congruent care to establish the effect on quality of life were obtained from literature reviews on effectiveness of each of the distinct interventions, as described in the evidence-based guideline. The stepped-care scenarios describe the resource use and accompanying effects on quality of life that will differ from usual care.

For comparison we described and valued CAU-reference scenarios based on a selection of large empirical databases from the Netherlands. Population-based cohort data were derived from the Netherlands Mental Health Survey and

Incidence Study (NEMESIS; Spijker et al. 2002; Kruijshaar et al. 2005; Smit et al. 2006; Cuijpers et al. 2007a). Empirical data on the use of care in the Netherlands Information Network of General Practice (LINH) database of longitudinal data on prescribing and referral by general practitioners and in the Second National Survey of General Practice study were used (Nuyen et al. 2008; Braspenning et al. 2004; SFK 2007; CVZ 2008; Gardarsdottir et al. 2007). Data were also derived from the control arms of clinical trials that measured the costs associated with depressive disorder for at least one year as well as empirical studies with a distribution of mild versus moderate and severe MDD (Bosmans et al. 2008; Stant et al. 2008; van Roijen et al. 2006).

For each scenario, input parameters are the treatment interventions offered, the coverage as a percentage of patients of the target population, the effectiveness of the treatment interventions (in the stepped-care scenarios) or the mean value for quality of life (in the CAU-reference scenarios) and the estimated costs of care consumption. The coverage rates, (effect on) quality of life and costs estimates of the care consumption per scenario are described in the Results section.

8.2.6 The health-economic simulation model

The health-economic model compares the guideline-congruent stepped-care scenarios with the CAU-reference scenarios. This depression state-transition model simulates the health and economic impacts of interventions for varying depression severity levels. The state-transition model is suited to our study as it conceptualises the course of depression in terms of health states (at risk for depression, mild MDD, moderate and severe MDD, recovery from mild MDD and recovery from moderate and severe MDD) along with the probabilities of making transitions across these states including time dependent parameters leading to valid estimations for the compared scenarios (Siebert et al. 2012). The model was based on Van Baal et al. (2008) and has been applied in other studies (Mohseninejad et al. 2013; Berg et al. 2011). Van Baal and colleagues based their model on an established Australian model by Vos et al. (2005) and adapted it to the Dutch setting. For the purposes of our study, Van Baal's model was adapted to distinguish between mild MDD versus moderate and severe MDD and the corresponding transition probabilities between the health states. The model was further adapted to accommodate the various treatment scenarios. The structure of the depression state-transition model is depicted in Figure 3. A cycle of four weeks is applied (0-4 weeks, 5-8 weeks, etc.), allowing every month a transition to another health state. Each health state is accompanied by quality of life weights and costs. Probabilities that depend on duration in a certain state guide the transitions from one health state into another. That is, the longer the length of an episode of MDD, the lower the probability to recover. Also, the longer patients are recovered, the lower the probability of having a relapse or recurrence. Textbox 1 lists the assumptions and their justifications that underpin the model.

Basic interventions:
1. Psychoeducation AND
2. Active monitoring AND
3. Structuring of the day

Step 1

Choice based on patient preference and shared decision making

Choice from minimal interventions and self-management interventions:
Self-management
Bibliotherapy
Activity scheduling, Physical activity, Running therapy
Psychosocial intervention
Counseling

Evaluation at 3 months

Duration longer than 3 months

Sufficient response   **+**   **Relapse prevention**

Step 2

-

Addition to basic interventions and step 1 (based on patient preference and shared decision making) choice from:
Problem solving therapy (PST)
Brief therapy (BT)

Evaluation at 6 weeks

Sufficient response   **+**   **Continuation PST/BT**

Evaluation at 6 weeks

-

Step 3

Choice based on shared decision making

-   *Sufficient response*

+   **Relapse prevention**

Following the stepped-care algorithm for mild MDD starts with the basic and minimal interventions. At a duration longer than three months or a recurrent episode, the patient may choose to combine the basic interventions with either problem solving therapy (PST) or brief therapy (BT). When this step does not lead to sufficient treatment response a third step is indicated with psychotherapy (PT), which consists of (cognitive) behavioural therapy, interpersonal therapy, or brief psychodynamic therapy. When the third step does not lead to treatment response after four months, the guideline suggests to either switch to one of the other types of psychotherapy or to switch to antidepressants (AD). Insufficient response is indicated with a 'minus' sign; sufficient response is indicated with a 'plus' sign.

Figure 1   Stepped-care algorithm for mild episodes of major depressive disorder

8.2.7 Analyses

Healthcare perspective

All analyses were conducted from the healthcare system's perspective. Owing to a lack of quantitative evidence, we conservatively assumed that the guideline-congruent care has effects on recovery and risk of relapse similar to (and not better than) CAU (see Textbox 1).

QALYs

Quality adjusted life years (QALYs) are used in health research as a summary measure to evaluate overall health benefits of interventions. QALYs reflect the health state of a person in such a way that one QALY stands for one year of life in perfect health. The standardization of health outcomes with QALYs

enables decision makers to make comparisons across interventions, diseases or populations, and to decide on the willing to pay per QALY gained (Torrance & Feeny 1989). The effectiveness of guideline-congruent care following the stepped-care algorithms was modelled through the transition probabilities from one health state to another in cycles of four weeks (0-4 weeks, 4-8 weeks, etc.). Quality of life

Basic interventions:
1. Psychoeducation AND
2. Active monitoring AND
3. Structuring of the day

Step 1

Choice based on patient preference and shared decision making

Choice from minimal interventions and self-management interventions:
Self-management
Psychosocial intervention
Bibliotherapy
Counseling
Activity scheduling, Physical activity, Running therapy

Choice from:
CGT
GT
IPT
Brief psychodynamic therapy

Choice based on shared decision making:
- Psychotherapy
- Pharmaco-therapy

Pharmacotherapy (with supportive counselling)

Evaluation at 4 months

Evaluation at 4 months

Sufficient response

Sufficient response

+

Relapse prevention Individual reintegration

+

−

Step 1 has been repeated?

−

Repeat step 1

−

Step 1 has been repeated?

−

+

+

Combination therapy or Intensified treatment

Following the stepped-care algorithm for mild MDD starts with the basic and minimal interventions. At a duration longer than three months or a recurrent episode, the patient may choose to combine the basic interventions with either problem solving therapy (PST) or brief therapy (BT). When this step does not lead to sufficient treatment response a third step is indicated with psychotherapy (PT), which consists of (cognitive) behavioural therapy, interpersonal therapy, or brief psychodynamic therapy. When the third step does not lead to treatment response after four months, the guideline suggests to either switch to one of the other types of psychotherapy or to switch to antidepressants (AD). Insufficient response is indicated with a 'minus' sign; sufficient response is indicated with a 'plus' sign.

Figure 2   Stepped-care algorithm for moderate-severe episodes of major depressive disorder
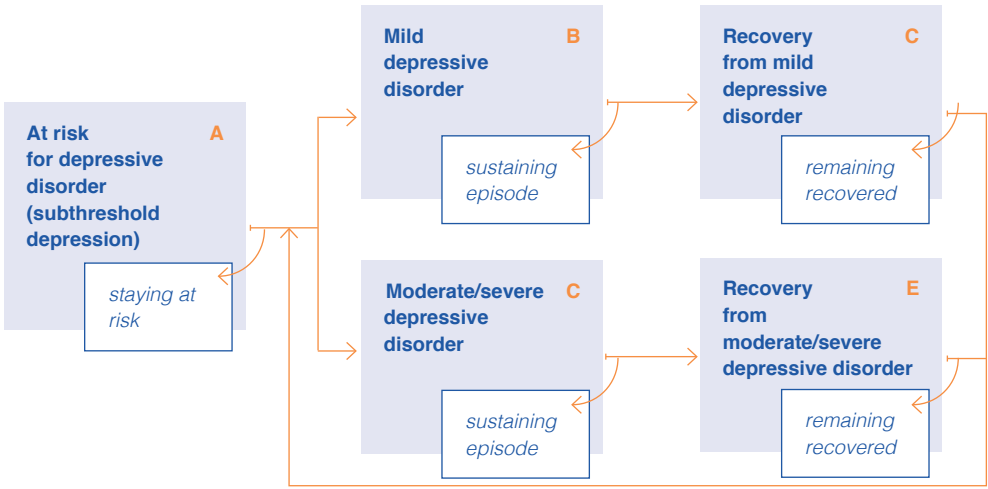
A person at risk for depression (state A) either stays in this state or develops a major depressive disorder (MDD) (states B or C). A person with an episode of mild depressive disorder (state B) either stays in this condition, recovers from this condition (state D). A person with an episode of moderate or severe depressive disorder (state C) either stays in this condition or recovers from this condition (state E). After recovery from a depressive disorder (state D or E) a person either stays in this state or has a recurrence (state B or C).

Transition rate 'a' is the probability of moving from being 'at risk' for depression (state A) to state B, a mild MDD; 'c' is the transition rate from being at risk for depression (state A) to moderate and severe MDD (state C); 'd' is the recovery rate from mild depressive disorder; 'e' is the recovery rate from moderate and severe depressive disorder.

Figure 3   Structure of the depression state-transition model

scores (utilities) for the different health states enabled us to perform a cost-utility analysis with incremental costs per Quality Adjusted Life Year (QALY) gained. Utility scores on a scale of 0-1 associated with the different health states based on preferences, with a higher utility for more preferable health states, were multiplied with the duration of time spent in that health state to result in total QALYs. Estimates of utility scores for states of MDD were calculated as 1-(disability weight) based on disability weights for respectively mild MDD (.19) and moderate or severe MDD (.51) as found by Kruijshaar et al. (2005).

Assumption	Justification
The depression state-transition model distuinguishes mild major depressive disorder from moderate or severe major depressive disorder.	In the classification of (major) depressive disorder (MDD) the depression severity can be specified as mild, moderate or severe (APA, 2013). For moderate and severe depressive episodes, treatment following the same algorithm is recommended (Spijker et al, 2013).
A cycle of four weeks is applied (0-4 weeks, 5-8 weeks, etc.), allowing a transition to another health state in every four weeks.	The cycle length is short enough to simulate the frequency of clinical events and treatment interventions (Siebert et al, 2012). Longer cycles introduce more bias (Chhatwal et al, 2014).
The probability to recover declines as the length of the episode increases. The probability to have a relapse or recurrence decreases over time since recovery.	The probability of recovery is decreasing as the length of the depressive episode increases (Spijker et al, 2002; Bockting et al, 2006). Recovery as a function of disease duration and relapse rates as a function of time since recovery were estimated on the NEMESIS study and an Australian modelling study (Werf et al, 2006; Vos et al, 2004), as described in Berg et al (2011).
We conservatively assume that treatment according to guideline recommendations does not result in a significantly faster recovery or lower chance of relapse or recurrence than care as usual.	The outcomes of treatment options can be split into 1) a direct effect, when the quality of life during a depressive episode improves as the number or severity of symptoms diminish; 2) an effect on recovery, when the duration of a depressive episode or the time to recovery shortens; and 3) an effect on relapse, when the probability of relapsing into a new episode of depression decreases. However, in the Dutch Multidisciplinary Guideline for Depression (Spijker et al, 2013) only quantitative evidence for the first effect can be found.
By comparing trajectories for different treatment choices, that is, with different quality of life weights per health state and costs, the direct effects of different treatment choices may be evaluated.	Treatment choices will impact on the quality of life and the costs of care (Andrews et al, 2004).
A 5-year time horizon is considered appropriate to capture the full effects in the scenarios and estimate the cost- effectiveness of the stepped-care and usual-care scenarios.	Since the treatment trajectories in the scenarios can take one year, and the time span of both the recovery probability curve and the relapse probability curve was two years, a time horizon of five years was chosen.

Tabel 1 Assumptions and justifications of the depression state-transition model

Effectiveness of the treatment interventions in the stepped-care scenarios were expressed as the standardized mean difference (i.e. Cohen's *d* and Hedge's *g* for small samples). The magnitude of Hedge's *g* and Cohen's *d* are interpreted using Cohen's convention as small (0.2), medium (0.5) and large (0.8) (Hedges & Olkin 1985). These standardized mean differences were mapped onto the utility scores in the MDD states in order to calculate QALY-effects. For this, as in previous studies (Lokkerbol et al. 2013), we followed Vos et al. (2004), by which a health gain of d=0.5 results in a corresponding health gain of 0.075 utility, using the conversion factor of 0.15 of Sanderson et al (2004). Comparing total QALYs for each scenario results in QALYs gained.

Costs

Costs of care in each scenario were estimated by multiplying the units of healthcare consumption with the unit's standard integral costing price as recommended (Hakkaart-van Roijen et al. 2015; Oostenbrink et al. 2000). The unit costs per type of care, with 2007 as reference year, are listed in Appendix Table 8S1. The time horizon for estimating the costs and benefits of the stepped-care scenarios relative to the CAU-reference scenarios was five years. In accordance with the Dutch guideline for economic evaluations in health care, after the first year, costs were discounted at a constant rate of 4% per year and future effects at a constant rate of 1.5% per year (Zorginstituut Nederland 2016). We indexed the costs to the year of 2017 as far as key outcomes are concerned by multiplying 2007 costs with a factor 1.166831113 based on the Dutch consumer price index obtained from Statistics Netherlands between 2007 and 2017 (http://statline.cbs.nl/Statweb).

Cost-effectiveness analysis

The incremental cost-effectiveness ratios (ICERs) express the cost-utility of the stepped-care algorithms as incremental cost per QALY gained.

For all scenarios we conducted probabilistic sensitivity analysis to assess the uncertainty around the incremental cost-effectiveness ratios and to ascertain the robustness of our results. The uncertainty ranges for the healthcare costs are described per scenario in Table 1 and in Appendix Tables 8S2 and 8S3. Uncertainty ranges for costs are the lower and higher bounds of estimations, with the peak estimations in the triangular distributions as the most likely value. The uncertainty ranges for the effectiveness of treatment interventions in the guideline-congruent care scenarios are given in Appendix Table 8S4. The distribution functions used in the probabilistic sensitivity analysis are also shown in Appendix Table 8S4. The probability curves for recovery and relapse used in the probabilistic sensitivity analysis, defined a priori, are reported in Van den Berg et al. (2011).

From the distributions of costs and effects in the depression state-transition model, parameter values for costs and effects were simulated in 5,000 runs. Probabilistic sensitivity analysis means specifying a joint probability distribution to characterise uncertainty in the model's inputs and propagating that uncertainty through the model to derive probability distributions for its outputs (Doubilet et al. 1986). The usual way to propagate the uncertainty in a probabilitistic sensitivity analysis is Monte Carlo simulation, that is to run a sufficiently large number of simulations (e.g. the 5,000 we choose), each with a different set of parameter values obtained by drawing random from the distributions around each of the parameter estimates (in Appendix Table 8S4). The resulting cloud of cost-effectiveness outcomes reflect the spread of ICERs. This approach is preferred because the ratio nature of the ICER outcome and the relative complexity of the underlying simulation model implies that analytic derivation of the correct confidence interval is mostly intractable.'

Cost-effectiveness acceptability curves were created to show the probability that following the stepped-care algorithms in comparison to CAU is cost-effective as a function of the budget that policy makers are willing to pay for gaining an extra QALY. According to Dutch guidelines, willingness to pay (WTP) reference values vary with the disability weight of a disorder between € 20,000 to € 80,000 per QALY (Zwaap et al. 2015). For depressive disorder, with a mean disability weight of 0.46 (Kruijshaar et al. 2005), this implies a maximum WTP of € 50,000 per QALY gained. A more conservative ceiling of € 20,000 per QALY (for disability weights between 0.10-0.40) is also reported. The health-economic modelling and related analyses were performed with the R software for statistical computing.

8.3 Results

8.3.1 Two guideline-congruent stepped-care scenarios

1 *Stepped-care for mild MDD, coverage rates and effectiveness*

While 50% of the patients with a depressive episode will recover within three months, for the remaining patients the episode duration is on average 6 months (Spijker et al. 2002). The scenario for mild MDD describes the first half year after starting with treatment when 40% of the patients (expert estimate) typically receives the basic interventions (effect size as in CAU) or, in 60% of the patients, patients receive both basic interventions and minimal interventions including bibliotherapy or (online) self-management (effect size d=0.84, 95% CI 0.65-1.02) (den Boer et al. 2004).

For mild MDD, guideline-congruent care includes monthly contact with the

general practitioner in step 1 and with both general practitioner and psychologist or psychotherapist in step 2, consisting of PST or BT (effect size d=0.83, 95% CI 0.45-1.21; Cuijpers et al. 2007b). In step 3, for the 20% of the patients (expert estimate) with a mild episode of MDD that have not recovered in step 2, first psychotherapy, then either psychotherapy or pharmacotherapy is prescribed. Subsequently, for the patients that do not benefit from either psychotherapy or antidepressants, combination therapy is indicated. For these patients, the care consumption can resemble CAU with a similar effect on quality of life and per-patient costs.

2 Stepped-care for moderate and severe MDD, coverage rates and effectiveness

For moderate and severe MDD treatment typically results in a remission of 76% (Spijker et al. 2002) while for the patients who will not be recovered, guideline-congruent care can resemble CAU. In the main scenario, guideline-congruent care includes contact with the general practitioner every two weeks and monthly antidepressant prescriptions during 8 months for 50% of the patients and for the other 50% contact with a psychotherapist (25%) or psychiatrist (25%) every two weeks (expert estimates). An effectiveness estimate for psychotherapy of g=0.531 (95% CI 0.345-0.717) was applied in the model (Haby et al. 2006; de Maat et al. 2007).

8.3.2 Care-as-usual reference scenarios

1 CAU for mild MDD, coverage rates and mean value for quality of life

In the reference scenarios for mild episodes of MDD, 42% of the patients (expert estimate) receive pharmacotherapy. The other 58% of the patients (expert estimate) receives a mix of care. In this scenario, the lower bound of the cost estimate of care consumption is equal to the estimate in the NEMESIS study (Kruijshaar et al. 2005). For the higher bound of the costs of CAU we estimated contacts with both the general practitioner and the psychologist or psychotherapist to take place every two weeks and prescription of antidepressant medication for 70% of the patients. The estimate of the effect as utility score .81 (fixed) (Kruijshaar et al. 2005).

2 CAU for moderate and severe MDD, coverage rates and mean value for quality of life

In the reference scenario for moderate and severe episodes of MDD, the 25% of the patients not improving in 32 weeks receive inpatient care, day care and homecare. The estimate of the effect as utility score is .49 (fixed) (Kruijshaar et al. 2005).

8.3.3 Healthcare costs of stepped care and usual care

Cost estimates of healthcare consumption in the scenarios for guideline-congruent care and CAU in the main analysis (mean cost estimates) and in the uncertainty analyses with lower and higher bounds of corresponding healthcare costs, are described in Table 1.

In the stepped-care scenario for mild MDD, the lower bound of the estimated costs of care consumption was based on a contact frequency of once in six weeks over a period of 6 months with these care professionals and the lowest estimation of care consumption in individual studies as discussed in meta-analyses including minimal interventions (den Boer et al. 2004) and PST or BT (Cuijpers et al. 2007b). The higher bound of the estimate of the costs of care consumption in mild MDD was based on contact with the care professional every two weeks and the highest estimate of care consumption in individual studies as discussed in these meta-analyses.

For moderate and severe MDD in the stepped-care scenario, the lower bound of the cost estimate is based on a consult with the general practitioner every four weeks, six prescriptions of antidepressant medication in 50% of the patients and no differences with the main scenario in contact with the psychologist, psychotherapist or psychiatrist. The higher bound of the cost estimate is based on weekly contacts with the general practitioner and eight prescriptions of antidepressant medication for 50% of the patients and monthly contact with the psychologist or psychotherapist in 50% of the patients and with the psychiatrist in 25% of the patients.

In the reference scenario for mild MDD, the lower bound of the cost estimate of care consumption is equal to care consumption in the NEMESIS study (Kruijshaar et al. 2005). For the higher bound of the costs of CAU we estimated contacts with both the general practitioner and the psychologist or psychotherapist to take place every two weeks and prescription of antidepressant medication for 70% of the patients.

In the reference scenario for moderate and severe episodes of MDD, cost estimates were obtained including and excluding care that is used by the 25% of the patients (expert estimate) not improving in 32 weeks (i.e. inpatient care, day care and homecare). This resulted in an estimate of the lower and higher bounds and the average costs of care for moderate and severe MDD.

Detailed descriptions of the coverage rates, type and amount of care consumption and corresponding costs in the guideline-congruent and CAU scenarios, with lower and higher bounds of the estimates in the main scenarios as used in the sensitivity analyses, are available as Appendix Tables 8S2 and 8S3.

8.3.4 Incremental effects

The incremental effects consist of the assumed effects on quality of life through treatment in the stepped-care scenarios compared to CAU-reference scenarios. Resource use and accompanying effects on quality of life that are assumed the same in the stepped-care and usual-care scenarios are ignored. The difference in treatment effects over the 5 year time horizon resulting from the simulations is a gain of 0.014492 QALY in mild MDD and 0.014831 QALY in moderate and severe MDD, implying modest but significant health gains (see Table 2 and Figure 4).

	Guideline-congruent care			Care as usual		
	Lower Bound	Peak	Upper Bound	Lower Bound	Peak	Upper Bound
Mild MDD	€ 254	€ 477	€ 693	€ 231	€ 401	€ 1049
Moderate-severe MDD	€ 906	€ 1113	€ 1736	€ 481	€ 850	€ 2019

Mental healthcare intervention costs in guideline-congruent care and care, for mild major depressive disorder (MDD) patients, and moderate-severe MDD patients. Peak (most likely) values with their lower and upper boundaries are given. Peak and boundary costs (in 2007 Euros) were estimated by an expert committee and modelled as a triangular distribution.

Table 1 Cost of care consumption in guideline-congruent care and care as usual for mild and moderate - severe major depressive disorder

8.3.5 Cost-utility analysis

The cost-utility analysis comparing differential treatment effects of the stepped-care algorithm for mild episodes of MDD versus CAU showed better health outcomes and less costs in favour of guideline-congruent stepped care, implying dominance of the guideline-congruent care. The cost-utility analysis comparing differential treatment effects of the stepped-care algorithm for moderate and severe MDD versus CAU suggested better health outcomes following the guideline-congruent stepped-care algorithm against more costs, with a mean ICER of € 2,700 (about € 3,200 in 2017 euro) per QALY gained. The incremental costs and effects and the Incremental Cost-Effectiveness Ratio (ICER) for the stepped-care scenarios are summarised in Table 2.

Results of the 5,000 simulated ICERs are presented in the cost-effectiveness planes in Figure 4 (left panel) with on the x-axis incremental utility (health gains in QALYs) and on the y-axis the incremental costs, both per person per year. The northeast quadrant displays health gains at additional costs and the southeast quadrant displays health gains accompanied by cost reductions. In all scenarios, 100% of the simulated ICERs fall into the right side of the y-axis, reflecting health

Depression severity	Incremental Costs	Incremental Effects (QALYs)	Mean ICER	ICERs in NE quadrant	ICERs in SE quadrant	ICERs in NW quadrant	ICERs in SW quadrant
Mild MDD	€ -36.72	0.014492	€ -2534	2.64%	67.36%	0%	0%
Moderate-severe MDD	€ 46.96	0.014831	€ 3166	67.16%	32.84%	0%	0%

Incremental costs, incremental effects (in Quality Adjusted Life Years - QALYs) and mean incremental cost-effectiveness ratios (ICERs) for mild major depressive disorder (MDD) and moderate-severe MDD. NE = North East, SE = South East, NW = North West, SW = South West. Costs are indexed to 2017 Euros. As can be observed from this table, guideline-congruent care leads to a negative mean ICER compared to care as usual, i.e. a relative gain in QALYs at lower costs. Hence, guideline-congruent care dominates care as usual in case of mild MDD. For moderate-severe MDD, a relative gain in QALYs with guideline-congruent care is achieved at somewhat higher costs.

Table 2 *Incremental costs, incremental effects and mean ICER for mild major depressive disorder (MDD) and moderate and severe MDD*

gains. The results show that in terms of the incremental costs per QALY, the stepped-care algorithms for both mild MDD and moderate or severe MDD are associated with greater health gains as compared to CAU.

For mild episodes of MDD, in 33% these health gains come with additional costs, while 67% of the simulated ICERs fall below the x-axis reflecting cost reductions, which suggests that there is a likelihood of 67% that stepped-care is associated with better health outcomes and lower costs, compared to CAU. The stepped-care approach is then deemed to be 'dominant' (i.e. to dominate CAU in terms of cost-effectiveness). For moderate and severe episodes of MDD, in 67% health gains come with additional costs, and stepped care is less expensive than CAU in 33% of the simulated ICERs.

The cost-effectiveness acceptability curves in the right panel in Figure 4 show that when applying a relatively modest WTP threshold of € 10.000 per QALY, the probability that the stepped-care algorithm for mild episodes of MDD is cost-effective is above 95%. For moderate and severe episodes of MDD, the cost-effectiveness acceptability curve shows a 80% probability that stepped care is cost-effective for a WTP threshold of € 10.000 per QALY. When applying an acceptable threshold of € 20.000 per QALY, both stepped-care algorithms have a probability above 95% of being cost-effective compared to CAU.
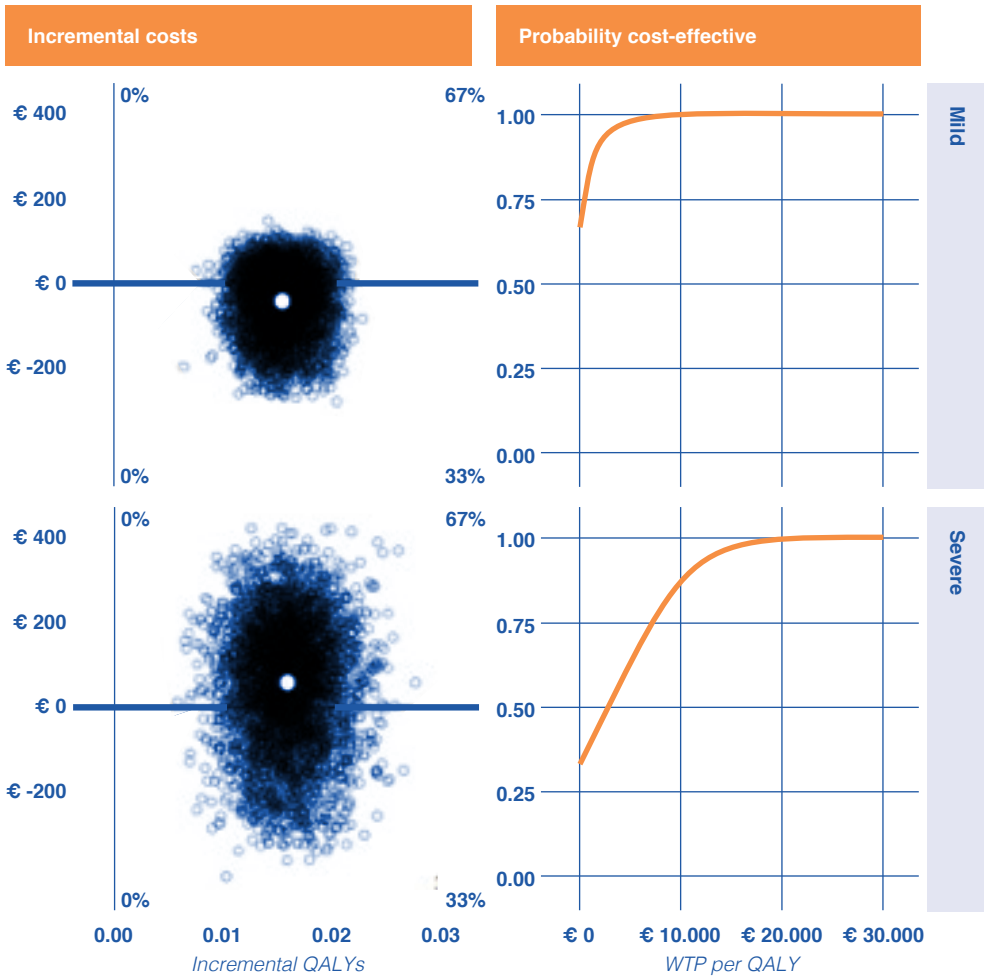
Left panel: Cost effectiveness planes with incremental effects in QALYs (on the x-axis) and incremental costs in € (on the y-axis) in the stepped-care scenarios versus care as usual for mild MDD (upper left) and moderate and severe MDD (lower left). Right panel: Cost-effectiveness acceptability curves showing the chance (P) that applying the stepped-care algorithm is cost-effective (on the y-axis) in € per QALY, for various willingness to pay (WTP) ceilings (on the x-axis) for mild MDD (upper right) and for moderate and severe MDD (lower right).

Figure 4 *Cost-effectiveness planes and acceptability curves for stepped-care versus care as usual for mild major depressive disorder (MDD) and for moderate and severe MDD*

8.4 Discussion

8.4.1 Main findings

This modelling study shows that health gains can be achieved cost-effectively following stepped-care algorithms according to clinical guideline recommendations.

The model simulations suggest that stepped care compared to usual care for mild MDD results in better health outcomes against lower costs in favour of guideline-congruent stepped care (dominant). For moderate and severe MDD, one extra QALY is gained at relatively low costs of on average about € 3,200 (in 2017 euros) for guideline-congruent care compared to CAU. The sensitivity analyses show that the results are robust. This implies that it is highly likely that stepped care is a cost-effective choice compared to CAU at acceptable willingness-to-pay (WTP) levels per QALY gained.

Our hypothesis, that in stepped care health gains can be achieved cost-effectively, was confirmed. The results from our cost-effectiveness analyses were not only due to differences in costs. The sensitivity analyses supported the robustness of the additional health benefits of the stepped-care scenarios; these were small, but positive in all sensitivity analyses. Apparently, for moderate or severe MDD, stepped care resulted in more intensive treatment regimens, i.e. higher costs, but also yielded clinically relevant effects over and beyond usual care.

Our depression state-transition model analyses are in line with previous findings in other cost-effectiveness studies evaluating depression guideline recommendations. The Improving Access to Psychological Therapies (IAPT) stepped-care approach based on the NICE guideline was associated with small gains in QALY and resulted in an ICER of £ 29,500 per QALY (Mukuria et al. 2013). Although surrounded with uncertainty around the costs and outcome, the IAPT service was within the NICE threshold of £ 30,000 per QALY. A modelling study in the UK comparing pharmacotherapy with cognitive-behavioural therapy (CBT) and combination treatment for moderate and severe depression in secondary care found that CBT as monotherapy was most likely to be the most cost-effective treatment option above a threshold of £ 22,000 per QALY with an incremental cost-effectiveness ratio of £ 20,039 per QALY compared with pharmacotherapy (Koeser et al. 2015)

8.4.2 Limitations of this study

Any modelling study depends on the accuracy of input parameters and model assumptions. Although we made all assumptions conservatively, there are several limitations we should mention.

First, the depression state-transition model is based on the Australian model of Vos et al. (2005), which was adapted for the Dutch situation. The current model and its outcomes can therefore not be generalised to healthcare systems in other countries without knowing that in usual care in the Netherlands all patients have universal health insurance coverage and fair access to a range of treatments for depressive disorder.

Second, the number of studies on effect sizes specified for the severity of the depressive disorder (mild versus moderate and severe MDD) was restricted. We based the estimations of the effect sizes on a limited number of treatment outcome

studies. Therefore, we applied probabilistic sensitivity analyses with conservative uncertainty ranges around the effect sizes.

A patient's future relapse and recurrence rate increases with the number as well as the duration of depressive episodes while treatment interventions differ in effect on the probability of recovery or relapse (Bockting et al. 2015; Beshai et al. 2011). However, evidence about how duration of the depressive episode or the number of recurrent episodes relates to treatment effects, is lacking. Therefore, we did not model the disease history regarding the number of depressive episodes, but we did model the effect of duration of depressive episodes on recovery and relapse. The model conservatively assumed that stepped-care strategies and usual care have similar recovery and relapse rates. The modelled scenarios are an underestimation of the true effects when the guideline recommendations do not only impact on quality of life but also improve recovery and/or reduce relapse rates, for example, through better adherence by care professionals, better compliance by patients to their treatments or lower drop-out rates.

Furthermore, according to the Dutch multidisciplinary guideline, observed partial recovery is informing clinical decisions on continuing treatment or stepping up to then more appropriate treatment. Also, it is known that the pathway to complete recovery runs via partial recovery (Spijker et al. 2002; Bockting 2006). Currently available data do not allow modelling the transition rate from mild MDD to moderate or severe MDD. Although conceptually desirable, the present model makes no distinction between partial and complete recovery and in that sense is not reflecting guideline-congruent care, which is a limitation. However, an augmented number of health states in the depression-state transition model would introduce uncertainty while evidence on the costs and effects distinguishing partial and complete recovery is still limited.

We restricted the costs to direct healthcare costs, which limits our findings. When different effects on productivity between guideline-congruent care and usual care were assumed, the impact on our results would be limited. However, not including the indirect costs may lead to underestimation of the wider costs of depression (Mohseninejad et al. 2013; Andrews et al. 2004). In case the step-up treatment would in line with clinical results be accompanied by improved participation, the cost-effectiveness would obviously have turned out more favourable.

Costs for monitoring and treatment evaluation, needed for timely stepping up to subsequent interventions were included in the contact with the care professional. Implementation costs, such as for costs needed to deliver interventions without waiting lists as part of an integrated care model, programme management and administration, training and supervision, strengthened logistics and information systems (Chisholm et al. 2016), were not included in the cost calculations. On the other hand, all assumptions in our modelling study were made conservative, resulting in cautious estimates of the possible effects of following guideline recommendations.

It is questionable whether the basic interventions, consisting of 1. psychoeducation, 2. active monitoring, 3. structuring of the day, are current care as usual or not. In our study we assumed that they are not. If these basic interventions could be considered as usual care, the costs of usual care would increase, indicating that our analyses were conservative.

The stepped-care scenarios describe appropriate and acceptable care according to current guideline recommendations. These scenarios represent an ideal model of care and at the same time an abstraction of real care in which it is not possible to take account of all relevant individual differences. Therefore, these depression state-transition model analyses need to be considered as indicative, giving the picture for the average patient.

8.4.3 Implications for clinical practice

This study lends support to the idea that guideline-congruent care is likely to be more cost-effective than usual care. Hence, wider implementation of guideline-congruent care and facilitating care professionals to follow guideline recommendations may be encouraged. From studies on implementing these guidelines we know that treatment processes can be improved, but also that guideline implementation is complex (Hermens et al. 2014; van Dijk et al. 2013; Richards et al. 2012; Franx et al. 2009; 2014). In clinical practice, treatment decisions made by shared decision making, for example on the choice between psychotherapy or pharmacotherapy in severely depressed patients, can be informed by the stepped-care algorithms. To recognise patients who will not benefit from a lower-intensity intervention or for whom treatment delay could cause harm, close monitoring and evaluation of expected and observed treatment response is required.

The stepped-care algorithms account for depression severity, depending on the nature and number of symptoms, while allowing for stepping in based on patient preference, treatment history or other patient variables. Better treatment outcomes are expected when care is more personalised to the patient's needs. However, it is currently unclear which patient variables can be matched to treatment to establish desired patient outcomes, such as the number of depressive episodes. Future research is needed to adjust the stepped-care algorithms accounting for this heterogeneity.

This study revealed that stepped-care algorithms can be used as cost-effective decision support tools for clinical decision making adjusted to patient's needs. The algorithms for mild episodes of major depressive disorder will reduce over-treatment and inappropriate use of antidepressants, while the algorithms for moderate and severe major depressive disorder aim to offer adequate treatment as soon as possible while reducing under-treatment.

8.4.4 Conclusions

Based on our study we may conclude that adhering to the stepped-care algorithms is associated with health improvement. It is very likely that the stepped-care algorithms following the depression guideline recommendations are cost-effective relative to usual care for depression. The extra costs per QALY of the stepped-care algorithm for mild episodes of MDD are with more than 95% certainty lower than € 10,000. The extra costs per QALY of the stepped-care algorithm for moderate and severe MDD are with more than 80% chance lower than € 10,000 and with more than 95% chance lower than € 20,000. This implies that guideline-congruent care is acceptable from a cost-effectiveness perspective. Our findings supports clinical decision making guided by stepped-care algorithms that are congruent with current guideline recommendations.

Chapter 9
General discussion

"Every individual matters.
Every individual has a role to play.
Every individual makes a difference."
Jane Goodall, c. 2000

The promise of stepped care is to simultaneously achieve better treatment outcomes for individual patients (a microperspective), integrated service delivery (a mesoperspective), and improved cost-utility in allocating care (a macroperspective). With this thesis, we aim to advance care for patients with depression in the expectation that this will be beneficial for individual patients, and will improve public health as well.

We investigated if stepped care can add value to depression care by: supporting clinical decision making with regard to the diagnostics and treatment of depression (aiming for better treatment outcomes for individual patients); improving the quality of depression care (aiming for integrated service delivery); and exploring the cost-utility of depression care (aiming for equity in allocating care). In this general discussion we summarise the main findings and examen what this thesis adds to the body of knowledge. Next, we will discuss some theoretical and methodological considerations and limitations we encountered during our studies, and recommendations for further research. Finally, we discuss the implications of this thesis in view of the current care debate and give recommendations for clinical practice and care policy.

9.1 Main findings and what this thesis adds

We summarise the main findings of this thesis by answering the research questions raised in the General introduction of this thesis and describing our scientific contributions, as follows.

9.1.1 A microperspective

What are the core elements of stepped-care strategies for depression?

Stepped care is, as introduced in chapter 1, in the first place a treatment strategy for decision making under uncertainty on what intervention will be most beneficial

for a certain patient. Stepped-care strategies seem applicable any time a judgement needs to be made on when and how to intervene, whenever evidence on a specific patient-treatment match is lacking. Stepped care, in this thesis, supports care professionals in the decisions to be made in the choice of the best treatment, for each patient with a depressive disorder. Essential is that stepped-care strategies are personalised, in recognition of the patient's profile.

The core elements of stepped-care strategies concern intensifying care according to the patient's needs: 1. Choosing the least intensive intervention to reach individual treatment goals, while taking into account the nature, duration, severity and course of the depression symptoms; 2. Routinely monitoring the severity and course of depression symptoms and periodically evaluating treatment and its observed outcomes; 3. Adjusting the individual treatment strategy by stepping up to a more intensive treatment, until treatment goals are reached.

When treatment goals are achieved, for example when remission is reached, this strategy is repeated for new or other treatment goals, such as relapse prevention, or personal recovery. Stepped-care heuristics, such as stepped-care algorithms, can provide an explication of the clinical decisions care professionals and their patients have to make. What stepped care adds to shared decision making is the responsibility to choose care that is appropriate and acceptable for the patient, while explicitly avoiding over-treatment and under-treatment, as explained in chapter 2.

How can depression care management advance individual stepped-care strategies?

Depression care management can advance individual stepped-care strategies mainly in three ways. Firstly, at all stages of depression, timely recognition of symptom severity and course, and subsequent careful monitoring and evaluation of measurable outcomes are central to both depression care management and stepped-care strategies. The depression care management process model, introduced in chapter 3, describes how feedback loops can operate between the patient level (microperspective) and the care process level of service delivery (mesoperspective). When of clinical relevance, steering information can serve as input in an improvement cycle for individual care.

Secondly, evidence-based clinical guidelines and other quality standards of care or decision support tools, can contribute to achieving better treatment outcomes for individual patients (microperspective). Their use and embeddedness in clinical practice is promoted by depression care management strategies (mesoperspective). This may improve the quality of service delivery. The three empirical studies in our thesis illustrate how improvement strategies on quality of service delivery (the mesolevel in the depression care management process model) can result in improved patient outcomes (the microlevel in this model).

Thirdly, an integrated service delivery design, with high quality care and efficiency of care processes, can improve conditions for care professionals to perform individual stepped-care strategies and can reduce uncertainty in clinical decision making.

9.1.2 A mesoperspective

What can be the added value of stepped care in depression care management?

Aiming to deliver care as efficient as possible, stepped care fits well with depression care management, as chapter 3 describes. Important components in this coordinated approach to patient care are, according to the Chronic Care Model: i) self-management support, ii) delivery system design, iii) decision support, and iv) clinical information systems. Stepped care can strengthen depression care management, in keeping with the patient's needs.

Supported self-management is often allocated as a first-step intervention in stepped-care models of care. Throughout following treatment steps, supporting the patient in self-management can contribute to personal recovery.

Stepped care provides a guiding principle for designing service delivery and allocating resources for care. Coordination of integrated care processes across the care continuum can be accomplished by structuring evidence-based interventions in a sequence of treatment steps of increasing intensity that are expected to benefit the patient, with explicit criteria for monitoring, evaluating and stepping up.

Evidence-based guidelines and standards of care, and the decision tools derived thereof, can support clinical decision making. When care processes are delineated on the basis of evidence-based clinical guidelines and standards of care, this also supports clinical decision making.

Clinical information systems provide timely and relevant data (both at the individual patient and aggregated level) to facilitate effective and efficient care. In this way, routine monitoring and periodic evaluation of care processes, is fundamental in depression care management. In stepped care, the focus of monitoring and evaluating care processes within healthcare organisations is then on improvement of individual treatment strategies and patient health gains.

To conclude, a stepped-care approach adds value to depression care management in several ways. The measured outcomes of stepped-care strategies are of relevance to the patient, while also for improving the quality and efficiency of the healthcare delivery system. This is crucial to create value-based health care.

Is it feasible to implement a stepped-care algorithm in depression care?

Delivering stepped-care strategies in the treatment of depression is supported by the availability of a predefined sequence of interventions that are expected to benefit the patient. In addition, this is supported by explicit criteria for monitoring, evaluating and stepping up.

The study presented in chapter 4 evaluates the implementation of a stepped-care algorithm for depression. This algorithm was supported by a liaison-consultation function in which a general practitioner could ask consultation from psychiatrists and psychotherapists from a Mental Health institution. Adherence of general practitioners and consultant care professionals to the stepped-care protocol proved to be 96% in our pre-post study in a pilot region, which was assessed by interviewing 28 care professionals of 235 patients with mild, moderate, or severe major depression. The percentage of patients referred to specialised care decreased significantly from 26% to 21% (p=.0180), allowing more patients to complete their treatment in the primary care setting. Moreover, requests for consultation by general practitioners became more concordant with the stepped-care protocol. We conclude that implementation of a stepped-care programme for depression is feasible in a primary and secondary care setting and is associated with fewer referrals to specialised mental healthcare services. This was the first study in the Netherlands to systematically evaluate the feasibility of a stepped-care programme for depression.

Is stepped care acceptable for care professionals and patients and can it lead to quality improvement on the mesolevel?

For the study in chapter 5 a pragmatic stepped-care depression model introduced different levels of care. This model consisted of a care pathway with a first-step for patients with brief or mild symptoms of depression, and a second-step for patients with severe depression. In this study the uptake of the Dutch Multidisciplinary Guideline for Depression in the primary care setting improved, as well as the multidisciplinary teamwork between mental healthcare professionals within and between primary and specialty care settings. We conclude that a stepped-care approach is acceptable for patients and care professionals. The introduced behaviour change required for starting to differentiate according to depression severity, offering new and less intensive treatment and monitoring depression symptoms, was perpetuated by care professionals throughout the change period, and continued after the project in most teams.

Thirteen multidisciplinary teams with 101 care professionals were involved in this study. The course of depression symptoms and treatment response were monitored using the Beck Depression Inventory (BDI) until recovery (defined as a BDI-score of 10 or lower) over a period 6 months. Twothirds of the patients (66%; n=356 patients) were considered non-severely depressed while 180 patients

(34%) showed severe symptoms. The overall mean percentage of non-severe patients treated according to the stepped-care model was 78% (range 53-100%). This proportion of non-severely depressed patients receiving a first step treatment according to the stepped-care model improved significantly during the project. In the severely depressed group 57% (range 25-100%) of the patients was treated according to the stepped-care model. This number includes 23 patients who were referred to specialty care within 1 month. However, 43% of the severely depressed patients did not receive antidepressant treatment or psychotherapy within 1 month or were offered treatment options of a too low intensity. Apparently, it is easier to apply the pragmatic stepped-care model for the non-severe patients than for the severly-depressed patients, but unknown is for what reasons. Probably, more organisational change is needed to avoid under-treatment and overcome provider barriers that were obstacles to diagnose and start treatment adequately within the one-month period for a substantial proportion of the severely depressed patients.

Succesful elements in the implementation were top-down goal setting, offering practical tools, standards and a set of clear instructions for the general practitioners on new and less intensive treatments, instead of offering antidepressants by routine. Also outcome monitoring using the BDI was a succesful element, shifting the focus of professionals from their own clinical judgements to more objectively assessed outcomes that could also be shared with others.

Can a self-help intervention for comorbid depression and anxiety disorder be implemented in diabetes care?

Self-help interventions for depression may constitute an appropriate first step as part of a stepped-care model for depression comorbid with diabetes mellitus type 2. Chapter 6 shows that a self-help intervention can be successfully implemented and integrated in diabetes care within a disease management framework, aiming to overcome under-recognition and under-treatment of depression and anxiety in patients with diabetes. We developed tools for diabetes nurses to perform the screening for depression and to provide suitable self-help interventions, or to refer patients to more specialised mental health care. More specifically, we trained diabetes nurses in the primary care setting to perform screening for depression and anxiety and to guide a self-help intervention focussed on psychosocial aspects of depression or anxiety in collaboration with both the patient and GP. In this study, 7 general practices, 7 nurses and 73 general practitioners participated. Of the 111 consenting diabetes patients, fifty-five were screened positive for depression or anxiety, and 26 screen-positives met the diagnostic criteria for depression and/or anxiety disorder as established with structured diagnostic interview by a trained researcher. Of these, 16 started and 15 completed the guided self-help intervention.

Measured with the Patient Health Questionnaire, anxiety symptoms improved significantly (3.2 points improvement; p=0.011), depression symptoms 5.7

points (5.7 points improvement; p=0.007), and somatic symptom severity 2.9 points (2.9 points improvement; p=0.041). Diabetes-related negative emotions (PAID-NL) dropped 3.8 points (p=0.048). The overall self-rated health status measured with the Visual Analogue Scale (range 0-100) of the EQ-5D improved by a mean of 14 points (p=0.007). Emotional role-functioning (SF-36) showed 33.4 points improvement (p=0.010), physical role functioning improved with 40 points (p=0.007), and emotional well-being with 19.4 points (p=.003). Patients' depression and anxiety symptoms as well as diabetes-related distress reduced after treatment with the guided self-help intervention, while the health profile and the mental component of quality of life improved. These findings suggest that the improvement strategy at the mesolevel of care, consisting of implementation of self-management guided by nurses and decision support for nurses, can result in a range of improved patient outcomes. Also, trained nurses demonstrated a greater competency at screening and at treating emotional problems in diabetes patients when facilitated by a validated screening questionnaire and a self-help intervention protocol. Close involvement of general practitioners seemed to be a relevant factor in the acceptance of these roles for nurses.

9.1.3 A macroperspective

What is the effectiveness of depression management programmes? Can the heterogeneity in outcomes be explained by clinical diversity?

Care management programmes that originate from the Chronic Care Model (CCM) take account of the pressure on quality and costs of care for chronic diseases. To provide a solution to the challenge of achieving affordable and high quality depression care, understanding what elements of these programmes are essential in establishing effectiveness is pivotal. However, the different chronic care management programmes for depression show variation in effectiveness, and this heterogeneity in outcomes limits insights for policy-making and programme planning.

Our systematic review and meta-regression analyses, in chapter 7, aims to explain the clinical diversity (i.e. variation in patient characteristics in the study population) and methodological heterogeneity (i.e. methodological study quality, length of follow-up and number of included intervention components according to the CCM) related to the effectiveness of chronic care programmes for depression. Included studies vary widely on chronic care management strategies for depression, such as guideline-based care, nurse-led interventions, self-management, collaborative care, community-based interventions and stepped care. One common aspect of these programmes is their strong focus on quality of care processes to improve the management and outcomes of depression.

Our systematic review draws positive conclusions about the effectiveness of chronic care programmes for depression overall. All reviews included in our

meta-analysis that reported on improvement of depression severity or treatment response showed positive results. Pooled effects of depression management programmes compared to usual care showed significant improvement in treatment response (RR=1.38; p<0.05) and in treatment adherence (RR=1.36; p<0.05). The results on costs were less convincing; while one review found that costs of enhanced quality care increased compared to care as usual but within the acceptability range of public health improvements (Neumeyer-Gromen et al. 2004), another review concluded that improved outcomes are associated with increased direct healthcare costs (Gilbody et al. 2006). In addition, it remained unclear which specific interventions or components are most (cost)effective.

Our subgroup analyses showed several significant improvements that were tested by meta-regression analyses. Studies of good quality showed significant improvements in our subgroup analyses on treatment response (RR=1.39; 95% CI: 1.12-1.73; I^2=88%), whereas studies of moderate quality did not. In our meta-regression analyses, this relationship was confirmed with study quality explaining a substantial amount of heterogeneity in treatment response (36.6%; p=0.04).

Subgroup analyses on patient characteristics showed that the significant effect of chronic care management in major depression (RR=1.24; 95% CI: 1.09-1.41; I^2=36%) was less strong than in minor depression (RR=1.88; 95% CI: 1.46-2.42; I^2=0%). In the meta-regression analysis, depression severity did explain a substantial amount of heterogeneity in treatment adherence (88.7%; p=0.01). Whether it is more difficult for patients with major depression to comply to any treatment, or to the appropriate more invasive treatment, or for care professionals to be adherent to adequate antidepressant prescription recommendations for these more severe patients, remains unclear. However, this finding suggests that efforts to improve patient compliance or adherence of the care professional contribute to maximising the effectiveness of chronic care management, especially for patients with major depression. Other aspects of clinical diversity, such as comorbidity, personal history, stage of life, or other patient characteristics, should be investigated as potential sources of heterogeneity.

Are stepped-carecs strategies, according to the Dutch evidence-based guideline recommendations, beneficial in term of cost-utility?

Clinical guidelines for major depressive disorder recommend preferably cost-effective stepped-care strategies for sequencing evidence-based treatments. In chapter 8 we evaluate the cost-utility of stepped-care algorithms according to the Dutch multidisciplinary guideline for depression in comparison to care as usual. The algorithms for mild episodes of depression aim to reduce over-treatment and the inappropiate use of antidepressants, while the algorithms for moderate and severe depression aim to offer adequate treatment as soon as possible, while reducing under-treatment.

With a health-economic state transition model we simulated health resource utilisation in a patient population across a range of depression severity levels, distinguishing between mild versus moderate and severe major depressive disorder, looked at corresponding healthcare costs and health gains expressed in quality adjusted life years (QALYs). The modelling study showed it most likely that health gains can be achieved in a cost-effective way following stepped-care algorithms, which are in accordance with guideline recommendations. The model simulations suggest gaining one QALY comes at a cost of € -2,500 (dominant) per QALY for mild depressive disorder when offering stepped care as compared to care as usual. The cost is € 3,200 per QALY for moderate and severe major depressive disorder. At an acceptable willingness-to-pay ceiling of € 20,000 for gaining an additional QALY, the stepped-care algorithms for both mild MDD and moderate and severe MDD are deemed cost-effective compared to care as usual, with a more than 95% probability. This implies that stepped care is quite likely a cost-effective choice when compared to care as usual. These findings support the current Dutch guideline recommendations, since the stepped-care algorithms appear to support clinical decision making under uncertainty in an effective and cost-effective way.

9.2 Theoretical and methodological considerations

9.2.1 Scope

This thesis entails a comprehensive scope, concerning the broad concept of stepped care. This thesis is not in-depth about the translation from the general to the particulars of individual patients in adapting treatment to the person, nor about the therapeutic relationship or the processes of intuition and reasoning in clinical decision making. However, this thesis offers starting points to relate to the fields of cognitive psychology and decision theory.

The improvement of care efficiency and equity in allocating care are important aims in the stepped-care model in this thesis, combining the meso- and macroperspective with the microperspective on depression care, as explained in Part I of this thesis. However, improvement of efficiency and equity is not part of the studies we performed in parts II and III.

The focus in this thesis is on how to support care professionals in clinical decision making for the direct benefit of patients with stepped-care heuristics to overcome uncertainty around the prognosis and progression of depression in a risk-averting way, avoiding over-treatment as well as under-treatment in individual treatment strategies. This thesis is also about quality improvement through stepped-care service delivery with care improvement strategies from a chronic care management approach.

9.2.2 Models in this thesis

The healthcare model studied in this thesis is a stepped-care model that combines a micro-, meso- and macroperspective on care.

Other models in this thesis are the comprehensive Chronic Care Model (in our studies in chapters 5 and 7) and the depression care management process model (introduced in chapter 3). For the cost-utility analyses in chapter 8, we used a state-transition model to simulate the health and economic impacts of guideline congruent care across a range of depression severity levels. This health-economic model distinguishes between mild versus moderate and severe major depressive disorder.

9.2.3 Study types

In this thesis several types of studies were used: narrative review, systematic review with meta-analysis and meta-regression analyses, three empirical studies with an uncontrolled pre-test post-test design, and a cost-utility study based on health state-transition simulation modelling. We regard it as an important strength of our studies that the interventions are congruent with the current Dutch multidisciplinary guideline (Spijker et al. 2013; Spijker et al. 2010), which is congruent with evidence-based clinical guidelines in other countries in many important aspects.

Since our aim was to pilot the effectiveness of stepped-care strategies and to test their feasibility, we opted for uncontrolled single-group pre-post study designs (chapters 4,5 and 6). This means that the effects that we observed may not have been caused by our intervention but by spontaneous recovery, or by factors that were not brought under control of the study. For example, highly motivated care professionals, their increased attention or increased frequency of patient contacts may have been the active ingredients that contributed in the observed positive effects.

The empirical study in chapter 4 was the first study in the Netherlands to develop, implement and evaluate a stepped-care algorithm with standardised treatment steps covering the whole continuum of care for depression based on evidence-based guidelines. We concluded from this study that is was feasible to implement a stepped-care algorithm for depressed patients in general practice. The effectiveness and feasibility of these algorithms were further studied in chapter 5, in a multidisciplinary care setting. This empirical study included a more elaborated data collection, with more participating care teams and nationwide coverage, albeit on a pragmatic stepped-care model with only two steps. In a quasi-experimental study with a naturalistic non-equivalent control group (Franx et al. 2014) the results of our uncontrolled study were confirmed. Changes in antidepressant prescription rates of primary care physicians participating in the

quality improvement project were registered over a period of three years. General practitioners in the multidisciplinary teams implementing the pragmatic stepped-care model significantly reduced their rates of antidepressant prescription over time, compared to general practitioners in a control group that were not exposed to the Breakthrough intervention. Also, Sinnema et al. (2015) conducted a tailored implementation programme in general practice, addressing key barriers for change by targeted interventions. This implementation programme led to recognition of a higher proportion of patients presenting with anxiety and depression, with more consultations after recognition, and did not lead to more prescription of antidepressants or referral to specialist mental health services. Patients in the intervention group reported better accessibility of care and provision of information and advice.

In addition, controlled trials on stepwise algorithm-guided care for depression have been published, showing positive results. However, mainly pharmacological treatment algorithms were compared with treatment as usual (Vermeiden et al. 2018; Trivedi et al. 2004; Bruce et al. 2004; Flaherty et al. 1998). For example, Adli et al. (2017) found that a highly structured algorithm-guided treatment was associated with shorter time to remission and fewer medication changes than either treatment as usual or computerised medication choice guidance. A cluster randomised controlled trial comparing a complete stepped-care algorithm comprising pharmacological and cognitive behavioural treatment with treatment as usual also yielded superior effectiveness, especially in the short-term (Oosterbaan et al. 2013).

The uncontrolled pilot study on the diagnosis and self-management of comorbid depression in patients with diabetes mellitus in general practice (chapter 6) was, to our knowledge, the first study in the Netherlands to explore whether a chronic care management approach to comorbid depressive disorder could become part of regular diabetes care provided by nurses. This empirical study showed that diabetes nurses could perform the depression screening and guiding of self-management as a first step, which was effective in reducing depression symptoms. The results of our uncontrolled pilot study were corroborated by two later published randomized controlled trials in patients with diabetes mellitus and a comorbid depressive disorder. In these studies stepped-care interventions for the amelioration of the depression symptoms were compared with treatment as usual (Ebert et al. 2017; Stoop et al. 2015). These studies showed superior effects of the stepped-care intervention over the control condition at 6 months follow-up (Ebert et al. 2017; Stoop et al. 2015).

In chapter 7, we presented our meta-analysis on chronic care management. Studies on stepped care were included, but not exclusively. Also other studies that included at least one of the chronic care components were included, because our interest was in healthcare service delivery from a chronic care management perspective. We choose to follow this broader approach, as we did for diabetes,

heart failure and COPD (Elissen et al. 2012; Drewes et al. 2012; Lemmens et al. 2011). In our meta-analysis, all studies that followed a stepped-care approach were found to be effective (Araya et al. 2003; Fortney et al. 2007; Hedrick et al. 2003; Katon et al. 2002; Unützer et al. 2002). Meta-analyses that included only studies on stepped care have been conducted by Van Straten et al. (2015) and Firth, Barkham & Kellet (2015). These meta-analyses included two of the studies on stepped care in our meta-analysis on chronic care management (Araya et al. 2003; Unützer et al. 2002). Both reviews on stepped care (van Straten et al. 2015; Firth, Barkham & Kellett 2015) found all differences significantly in favour of stepped care, with small positive effects on depression outcomes. Because of the considerable variance in treatment steps, the number and duration of these steps, criteria for stepping up and professionals involved in the stepped-care interventions, the researchers in both studies conclude that the evidence that stepped-care treatment delivery is superior to care as usual, is still rather thin. Also, both reviews show considerable clinical heterogeneity (baseline severity, age, comorbidity) as well as methodological heterogeneity (depression criteria, samples, setting, control condition) in the included studies. New randomised controlled trials endorse the positive findings (Salomonsson et al. 2017; Rollman et al. 2017). In a narrative review, it was found that effective collaborative care adheres to the principles of stepped care (Unützer & Park 2012). In a corroborating meta-analysis and meta-regression analysis, Miller et al. (2013) found that no single component and no specific factors in the meta-regression analysis was statistically associated with the effectiveness of the Chronic Care Model, and that evidence supports stepped care application to more severely ill patients with mental health conditions. In a Cochrane review on shared care interventions for chronic disease management, particularly in studies examing shared care interventions with a stepped-care design, mental health outcomes improved in response to depression treatment (risk ratio (RR) 1.40, 95% confidence interval (CI) 1.22 to 1.62; six studies, N=1708) and recovery from depression (RR 2.59, 95% CI 1.57 to 4.26; 10 studies, N=4482) (Smith, Cousins, Clyne, Allwright & Dowd 2017).

We wanted to further study the positive findings of our uncontrolled studies on stepped-care algorithms in depression. This could have been done preferably with a cluster-randomised controlled trial in a larger population comparing the effectiveness of stepped-care algorithms with care as usual. It is however, methodologically complex to conduct such a controlled trial spanning the whole continuum of care in service delivery, in comparison to care-as-usual service delivery (see also our recommendations for further research). We have tried to overcome this problem by performing a modelling study, which was presented in chapter 8, based on existing data, as was suggested as by Bower & Gilbody (2005). Economic analysis of guideline recommendations supports decision-makers with the best outcomes from limited resources (NICE 2014). In our study, evidence from different sources was combined into a state-transition model, accounting for uncertainty and sensitivity to change in the model parameters and

the compared scenarios. Clinical practice guidelines that summarise the evidence-base, clinical expertise and the patient perspective, provide the best source for defining optimal care (Andrews et al. 2004). In the stepped-care algorithms in our study, evidence-based interventions, and the order steps in which these interventions are sequenced, are entirely based on established clinical guideline recommendations differentiating for depression severity. We found that stepped care is quite likely a cost-effective choice when compared to care as usual. This finding has been found also in several randomised controlled trials that have been performed on cost-effectiveness. These studies favour stepped care, showing that cost-effectiveness is at least equal to care as usual, or the higher costs are related to greater effectiveness (Simon et al. 2001; Katon et al. 2005; Araya et al. 2006; Simon et al. 2007; van 't Veer-Tazelaar et al. 2010; Mukuria et al. 2013; Koeser et al. 2015; Solomon et al. 2015).

9.2.4 Limitations of our studies

Our studies have the following methodological limitations. The study on the feasibility of a stepped-care programme for depression gathered data which were aggregated on the level of a participating mental health institution. Thus we could not describe the flow per patient through the programme. The aggregated data, however, showed that patients were treated in line with the stepped-care algorithm. A process measure was adherence of care to the stepped-care protocol. This was assessed by self-report in the semi-structured interviews on the question whether the care professional treats patients in accordance to the stepped-care protocol. This has probably resulted in overestimation of adherence. However, a variety of quantitative approaches to assess adherence in clinical practice encounters obstacles too, such as in the measuring of adherence to combinations of treatments or multidisciplinary treatment, or in measuring the influence of the interaction of the patient and the care professional (van Fenema 2016). Although our process measure was subject to bias, it provided insight into the knowledge of care professionals on the stepped-care protocol and its acceptability.

In the implementation study in chapter 5, self-report by care professionals on the implementation of the interventions leaves uncertain whether patients actually received care according to the protocol. Because we did not measure presence and severity of depression symptoms at patient level, we can not conclude anything with respect to symptom change. Despite these limitations, our study suggested that the quality improvement method promotes change in professional and organisational performance through implementing the multidisciplinary guidelines, and was successful in shifting attention to interventions other than pharmacological treatment.

In the diabetes pilot study, the number of participating patients remaining in the study was small (n=15). Moreover, the study sample was severely depressed, with

relatively low scores on the SF-36 compared to the Dutch general population or to patients with type-2 diabetes in general practice, and a high number of comorbid chronic somatic illnesses. Also, the applied screening procedure did not show a good positive predictive value, indicating that among those who had a positive screening test, the probability of depression or anxiety disorder was 49.1%. A more sensitive screening instrument is needed to improve case detection. In the recent literature, using screening for depression symptoms (PHQ-9) and anxiety symptoms (GAD-7) as recruitment also resulted in a small number of participants in a treatment trial for anxiety and depression in people with type 2 diabetes treated in primary care (Stoop et al. 2017). These researchers therefore question whether screening is followed by low uptake of treatment in primary care too.

Generally, a limitation of systematic reviews is that publication bias may occur. We have not conducted an analysis of publication bias, which could provide insight into the extend to which the pooled effectiveness was influenced by the likelihood of retrieval of the included studies due to non-significant intervention effects. Nevertheless, we followed a broad search strategy and an a priori established review protocol with four potential sources of statistical heterogeneity between the studies, based on literature, and the four most frequently reported measures of either processes or outcomes of depression care. Another limitation of the meta-analysis was that comparisons between the included studies were difficult to make because of the rather poor information on the operationalisation of the intervention components. Moreover, these studies showed a great variety of sometimes difficult to compare measurement instruments, such as for patient satisfaction or quality of life. When data were reported incompletely, or where not given for the control group, and could not be retrieved from the authors while recalculated estimations were impossible, studies were excluded from the meta-analysis.

As in any modelling study, our economic evaluation depends on the validity of the model assumptions, and the availability and precision of the values for input parameters. For example, due to limited evidence, our model could neither account for the longer-term effects of a history of previous depressive episodes, nor for the impact of partial recovery (with lingering residual symptoms) on outcomes such as time to remission and depression relapse before recovery. Also, the number of studies on effect sizes stratified for depression severity (mild versus moderate and severe depression) on which the model was based is limited. Therefore, we made all assumptions conservatively, strengthening the null-hypothesis of no superiority of stepped-care over usual care. The modelled scenarios of stepped care are therefore a likely underestimation of the true effect. However, by not including the indirect healthcare costs we may have underestimated the wider costs of depression under current care, as well as potential reductions under optimal care, as Andrews et al. pointed out (2004). Costs for monitoring and treatment evaluation, needed for timely stepping up to subsequent interventions were included in the contact with the care professional.

9.2.5 Recommendations for further research

Stepped care is implemented and evaluated in mental health care on a growing scale, as measured by the increasing number of studies over the years. To reach firm conclusions about effectiveness and cost-effectiveness we have the following recommendations for further research.

First, stepped-care treatment strategies are to be distinghuished from stepped care as a delivery system. For the evaluation of stepped care either as a treatment strategy or as a delivery system, it is important to distinguish the micro-, meso-, and macroperspective, and to clarify the corresponding aims that are relevant and understood from the perspective taken. Conclusions on stepped care in general should be made preliminary when only one aspect of stepped care has been studied.

Furthermore, in study design, we recommend that treatment steps, the several treatment interventions within each treatment step, the order in which they are sequenced, and the criteria for stepping-up, are in line with the evidence as summarised in clinical practice guidelines. In addition, since many published studies in this area evaluated minimal interventions for first or mild episodes of depressive disorder as a first step in a stepped-care model or programme, designing studies in which stepped care is covering the whole care continuum is recommended. These studies would include more specialised follow-up interventions for persisting, recurrent or more severe depression to enable patient-centred care across the care continuum. Also, to evaluate guideline-congruent care, these studies would include more treatment options within a treatment step.

Stepped-care service delivery is assumed to achieve at least equivalent clinical effects and improved efficiency compared to care as usual. Stepped care as a treatment strategy is assumed to achieve improved effectiveness against costs that offer good value for money. Fully powered equivalence trials testing these assumptions for stepped care spanning the whole care continuum, including psychotherapeutic interventions, are recommended.

A number of methodological and procedural uncertainties associated with the conduct of such large trials need to be encountered (Hill et al. 2014; Blanco, Raffull & Olfson 2013). Obstacles concern the study design, trial methods and procedures, recruitment and retention rates, the proportion of patients that step up from low- to high-intensity psychological therapy, and estimated treatment effects in sample size calculation.

The comparison group needs to be carefully chosen and well described, as well as the stepped-care intervention (Seekles 2011; Seekles et al. 2009; van 't Veer-Tazelaar et al. 2006). For example, what matching factors are integrated in the stepped-care intervention to triage patients to appropriate treatment? What matching factors are used in usual care? In a RCT comparing stepped care with either brief therapy or cognitive therapy as a first step to matched care, matched

care consisted of care as ususal (van Straten et al. (2006). Stepped care in this study was found at least as effective as matched care. To our knowledge no other controlled study directly comparing the effectiveness of stepped care versus matched care in depression has been performed (O'Donnell et al. 2016).

More research, with patient-related outcomes, is needed on the effectiveness of individual (micro-level) stepped-care strategies as well as on the efficiency of stepped-care delivery systems at the meso and macro levels. For example, studies on how to apply research data, such as derived from outcomes management (on the meso-level), to inform microlevel decision making in stepped-care treatment strategies, may contribute to implement personalised care (Tiemens, Bocker & Kloos 2016). Furthermore, evidence on the cost-effectiveness of stepped-care decision support tools for treating depression compared to care as usual is still limited. When randomised trials are not possible, modelling studies may be a good alternative.

To support clinical decision making (at the microlevel) the stepped-care algorithms offer heuristics for a timely and adequate treatment policy accounting for severity, duration and recurrency of symptoms. Further research is needed on how care professionals work with these heuristics in clinical reasoning and shared decision making (f.e. Delgadillo et al. 2015). Also, research is needed on the relevance of the role that other patient variables, treatment variables, organisational variables or contextual variables may play in dealing with uncertainty around the diagnosis, prognosis, effects and risks of treatment (f.e. Saxon, Firth & Barkham 2017; Firth, Barkham, Kellett & Saxon 2015). To aid patients in the process of shared decision making, decision tools need to be developed or updated, and evaluated (Elwyn et al. 2018). Also these patient decision tools need to take account of uncertainty and varying patient preferences (Kaltoft, Nielsen & Dowie 2018). When new research leads to the availability of other outcome predictors or matching variables, the stepped-care algorithms need adjustment accordingly.

9.3 Implications and recommendations for healthcare policy and practice

Today's topics in mental health care, in the Netherlands and abroad, concern finding solutions for providing good patient care with a perceived scarcity of resources in the face of growing financial and administrative pressures and increasing caseloads. While in the Dutch governmental coalition agreement for the period of 2019-2022 the total budget for health care is increased, the budgetary growth for mental health care is capped by a decreasing growth rate and constrained through framework agreements (Rutte et al. 2017). Also, the organisation and financing of care on the mesolevel is overtly affecting the microlevel of care. Agreements with care insurance companies about performance

targets and registration requirements may not always lead to the best treatment for an individual patient or for a group of patients. For example, when exceeding an agreed budget would imply that a certain evidence-based treatment may not be covered anymore for the rest of that year. As a result the appropriate intervention may not be delivered, the quality of care may diminish and waiting lists or patients stops may emerge. With the aim to advance depression care for the benefit of all patients and public health, we discuss the implications and recommendations that our studies may have, in service of the care debate on healthcare policy and practice related to these issues.

9.3.1 Matched care, the articulated alternative

When speaking of stepped care, we recommend to use the definitions that are provided in this thesis, distinguishing stepped-care treatment strategies and stepped-care service delivery. We think this recommendation is important since conceptual confusion around stepped care versus matched care still seems to exist (Zorginstituut Nederland 2017), which is not leading the debate on optimising treatment allocation (stepped or matched?) forward.

Stepped care and matched care are both concerned with how to match patient and treatment accounting for clinical diversity. From a matched-care approach, it is assumed that certain characteristics of individual patients are matching factors that can be identified prior to starting treatment in order to determine the best match. However, evidence for true matching factors is still poor, as discussed in paragraph 1.2.3. In the meantime, the evidence for stepped-care service delivery keeps growing (see also chapter 2). In their post-hoc analysis examining if treatment intensity during 1-year follow-up in patients with common mental disorders can be predicted prospectively by pre-treatment dispositional or need for care factors, Van Orden et al. (2017) could not identify a subgroup of patients that did not sufficiently respond to a short-time collaborative care treatment as a least intensive step in a stepped-care model. Advances in prediction research in search of moderator effects are being made in relation to stepped-care service delivery (Lorenzo-Luaces, DeRubeis, van Straten & Tiemens, 2017; Gunn et al. 2017; Bower et al. 2013). According to our definition, matched care and stepped care are not conflicting by nature at all (see chapters 1 and 2).

In our definition, stepped care sequences are not fixed. The sequence in which treatment options in our studies are to be considered and balanced, is in accordance with the Dutch multidisciplinary guideline and care standard for depressive disorder. The guideline-congruent stepped-care algorithms stratify for the nature, severity, duration and recurrency of symptoms. These important outcome predictors and determinants of patients' needs are matching factors in a stepped-care treatment strategy, which according to our definition, is not the same as a matched-care approach.

In shared decision making by means of the stepped-care algorithms, also treatment history of previous experience or outcomes of earlier treatment, comorbidity (somatic, interpersonal or psychosocial), other expected treatment effects (for example on sleeping), expected or occurring side effects or interactions, treatment outcomes in firstdegree family members, personal history, personal situation, or other patient characteristics, combined with patient preferences, can determine appropiate care (Meeuwissen, van Bon et al. 2018).

As long as evidence for true matching factors (that have a differential effect on specific treatments and can be identified prior to treatment, see chapter 2) is poor, while evidence for a pragmatic, 'fast and frugal' (as in Marewski & Gigerenzer, 2012) stepped-care approach is growing, stepped-care treatment strategies can add value to depression care.

9.3.2 Care improvement through outcome monitoring

At the meso- and macrolevel, in the Netherlands, the healthcare system is steered by external surveillance on quality control, and by care insurance and care market regulations. Responsible authorities impose requirements for quality control, or volume and coverage agreements. Quality indicators are applied for public control, for agreements of care insurance companies about performance targets or the quantity of care consumption that is covered, or in measurement of performance indicators to benchmark mental health services. We recommend that these quality indicators are attuned to indicators for internal quality improvement by care organisations, and that these indicators are of clinical relevance (Meeuwissen, Boomstra & Henkelman 2007). This entails that quality indicators used in the monitoring and the evaluating of care processes at the mesolevel, are chosen for criticial aspects of care on the microlevel (Meeuwissen, van Wijngaarden & Smit 2009). This way, outcome data can be applied to inform decision making in clinical practice and serve as input in an improvement cycle for individual care, as in stepped-care strategies. The strategic choice is to make individual outcomes of treatment the central focus in the continuous improvement process within healthcare organisations.

In the Netherlands, Routine Outcome Monitoring (ROM) is implemented top-down and it is obligatory for health services to supply ROM data to healthcare insurers to enable benchmarking. ROM is a method for repeated assessments of treatment outcome at regular intervals in order to monitor patients' progress during treatment through the systematic application of these assessments (de Beurs et al. 2011). But the implementation of ROM is mainly restricted to this obligatory part and takes place mainly at the start and the end of treatment. The use of ROM to obtain feedback on treatment progress and to adjust individual treatment policy based on the outcomes measured is limited due to the reported lack of clinical relevance of the assessment instruments and measurement time points (Nuijen et al. 2015).

Instruments in the ROM system are mostly not disorder-specific or do not measure relevant outcomes like recovery, wellbeing or quality of life at points in time when it could provide patients or care professionals with information relevant for deciding on continuation or change of treatment, in shared decision making or in peer consultation.

Routinely monitoring the progress of symptoms and evaluating treatment outcomes is essential in stepped care to adjust treatments (Von Korff & Tiemens 2000; chapter 2). To safeguard the clinical relevance of outcome monitoring, it is recommended that the monitoring and evaluation takes place at so-called critical decision points. When the goals of the evaluation are not met at such a decision point, the treatment is changed and stepped up. Tiemens & van Sonsbeek (2017) suggest that ROM should become more related to individual treatment goals and that monitoring should be performed with appropriate instruments at crucial points in time to provide feedback for patients and care professionals during the treatment process. In line with this, we recommend to apply the Dutch care standard for depressive disorders (Meeuwissen, van Bon et al. 2018; Spijker, Meeuwissen, Aalbers, van Avendonk, van Bon, Huson et al. 2018) that describes how patients and care professionals agree on explicit treatment goals and the treatment plan, how these are monitored and evaluated at clinically relevant time points in the treatment process, and how the treatment plan is adjusted as needed to reach the treatment goals. Clinical relevance should thus always be the guiding principle, in clinical management (at microlevel), as well as in outcomes management (at mesolevel) of healthcare service delivery. The measured outcomes of care should also be of relevance to the patient in order to create value-based health care (Porter 2010; 2008; Porter & Teisberg 2006).

9.3.3   Quality standards and the merits of clinical guidelines

In the Netherlands, inspired by the Chronic Care Model, standards of care (zorgstandaarden) are developed (Baan 2015). The care standard for depressive disorders (Meeuwissen, van Bon et al. 2018; Spijker et al. 2018) provides a framework for patients, care professionals and health policy makers, and describes high-quality care from the patient's perspective. Evidence-based guidelines are underlying the care standard. The care standard shares common ground with all parties involved in depression care and can facilitate to make agreements on quality or efficiency of care between these parties.

An important advantage offered with the availability of the care standard is that responsible authorities need no longer base policy decisions on the evidence-based guidelines. These guidelines have been developed and kept up-to-date to support clinical decision making in delivering appropiate patient care and to enable informed choices on treatment planning and shared decision making. The improper use of guidelines, for the purpose of external quality control, accountability, care

contracting and reimbursement, has been summarised by the Council for Public Health and Society (Raad voor Volksgezondheid en Samenleving, RVS) as the core problem in tensions around evidence-based practice (RVS 2017).

It is recommended to keep in mind that clinical practice guidelines have merits of their own. Studies on the implementation of the Dutch Multidisciplinary Guideline for Depression have shown benefit, especially on the organisational level of care (f.e. van Fenema 2016; Sinnema 2015; van Dijk 2014; Franx 2013). Clinical guidelines need to be preserved for what they were developed for. The development of care standards cannot replace clinical guidelines or make them redundant.

9.3.4 Person-centred mental health care

Evidence-based health care has been critisised for its reductionism based on mean outcomes in groups of patients, neglecting (transdiagnostic) variance underlying a diagnosis, the individual patient's characteristics or personal values, and the patient's context, that are all important in clinical practice (RVS 2017; Burgers 2017; van Os 2017; Cross & Hickie 2017; Greenhalgh et al. 2014; Gray 2013; Miles, Loughlin & Polychronis 2008). Whereas the evidence-base for depression treatment grows, attention for the personal and the context of the patient in deciding on which treatment to choose, and the realisation of person-centred care, stay behind (Miles et al. 2008; van Os 2017; Delespaul et al. 2016). This problem is also recognised by the Council for Public Health and Society (Raad voor Volksgezondheid en Samenleving, RVS, 2017). Evidence-based guidelines, developed with available literature, professional knowledge and patient experiences, intended to support care professionals in clinical practice and (shared) decision making, can enable person-centred care and a personal approach to patient care. Guidelines provide the reliable source of knowledge that is needed in person-centred care for care professionals and patients to make explicit and well-considered treatment decisions (Burgers 2017; McCartney et al. 2016; Greenhalgh et al. 2014).

At the microlevel, guideline-congruent care includes much more than treating patients with one of the evidence-based interventions in the guideline: monitoring and adjusting care based on individual patient outcomes, the relationship between patient and care professional, informed shared decision making, and taking into account personal or contextual factors, are needed to provide patient-centred care. Uncertainty appears to be inherent to decision making in depression care. To support clinical decision making under uncertainty, the stepped-care algorithms that were developed for diagnostics and treatment, supporting a timely and adequate treatment policy, seem of added value. It is recommended that to be able to improve adherence to guideline recommendations, these algorithms are implemented and evaluated as feasible heuristics in everyday clinical practice.

9.4 In conclusion

With this thesis we aim to advance care for patients with a depression by means of supporting care professionals with stepped-care strategies, and by outlining the conditions of stepped-care service delivery.

We distinguish stepped care as a treatment strategy from stepped care as a form of service delivery. In depression care, care professionals and their patients need to deal with uncertainty throughout the therapeutic process. Uncertainties that exist about the diagnosis, the prognosis and treatment risks and effects need to be accounted for in decision making. Expected benefits and risks of intervening or not intervening need to be balanced with patient preferences, values, and costs of care. Stepped-care treatment strategies can support care professionals (and their patients) in decision making under uncertainty, avoiding over-treatment as well as under-treatment, as described in this thesis. Stepped-care service delivery can contribute to reducing an amount of the uncertainty, as explained in this thesis.

Evidence for true matching factors (that have a differential effect on specific treatments and can be identified prior to treatment) is poor, while evidence for a pragmatic, 'fast and frugal' (as in Marewski & Gigerenzer 2012) stepped-care approach is growing. Outcome predictors and patient preferences are important for finding the best match between patient and treatment, serving treatment goals. The stepped-care algorithms stratify for the nature, severity (mild versus moderate or severe), course (recurrent or not) and duration (shorter or longer than three months; persistent or not) of depression symptoms. In shared decision making by means of the stepped-care algorithms, also other patient characteristics can determine appropriate care, such as outcomes of earlier treatment, comorbidity, expected or occurring side effects or interactions, personal history, personal situation (Meeuwissen, van Bon et al. 2018; Spijker et al. 2018).

The main conclusions of this thesis for healthcare policy and practice are, first, that stepped-care strategies are essential in obtaining optimal treatment outcomes for depressed patients and, second, when improving the quality of depression care at the meso- and macro level, it is crucial that the primary treatment process and the patient-level health outcomes are central, from a patient-centred view. Healthcare policy makers can improve depression care by shaping the conditions to perform stepped-care strategies. Care professionals can improve patient outcomes by applying stepped-care decision support tools for clinical decision making under uncertainty about the individual prognosis.

True matching factors that still may emerge, as well as outcome predictors, patient preferences and contextual factors that have been discussed as relevant matching factors, are to be integrated into stepped-care strategies.

Stepped care enables stratifying care to the patients's profile and a person-centred approach in daily practice. As long as this adds value to depression care, it holds that every patient with a depression is *the case for stepped care.*

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Appendices

Author, year of publication	Analysis type, number of studies included	Concept/definition of chronic care programmes	Inclusion criteria	Exclusion criteria	Author's conclusions
Frederick et al, 2007	Descriptive review; N=82 (77 RCTs/ CCTs, 1 pre-post study, 4 other designs).	Community based treatment of late life depression based on socio-ecologic model of healthy aging that suggests that community-based interventions operating at individual, interpersonal, institutional and policy levels may affect public health outcomes, in this case depression outcomes.	Studies were included when they addressed: mean age ≥60 year; total sample size ≥25; community-based setting; depression DSM-IV or assessment instrument score (as primary or secondary outcome); clearly described and replicable interventions including multifaceted and single level interventions. Studies with mean age <60 year were included if they reported data for ≥25 older adults.	Non-English articles, duplicates, reviews, meta-analyses, studies with inpatient or institutionalised patients, or conducted in a university based research center, and clinical studies of anti-depressant medication were excluded.	Depression care management was the only intervention rated as effective. It produced statistically significant results across both home- and clinic based models in 8 different RCTs with the largest number of participants among reviewed interventions. These interventions all involved identification of depressed individuals through a standardized screening, referral for active treatment and a close follow-up of participants.
Gilbody et al, 2006, Arch Intern Med	Meta-analysis; N=37 (37 RCTs).	Collaborative care defined as a multifaceted intervention involving combinations of 3 distinct professionals working collaboratively within the primary care setting: a case manager, a primary care practitioner and a mental health specialist; to be included studies had to involve 2 of these 3 components.	To be included in the review, studies had to be: RCTs with patients being managed in primary care settings using a collaborative care approach.	Not specified.	Collaborative care is more effective than standard care in improving depression outcomes in the short and longer terms.
Neumeyer-Gromen et al, 2004	Meta-analysis; N=10 (10 RCTs).	DMPs consisting of evidence based guidelines, patient/provider education, collaborative care, reminder systems and monitoring.	To be included in the review, studies had to be: RCTs; a complete DMP with all components (see definition); addressing all kinds of depression as primary diagnosis in adults above 18 years; with sum scores for the outcome variables available; with outcome measurements instruments of each study published in a peer-reviewed journal and filled-out by participants, their relations or independent raters.	Validity assesment: trial quality had to be A/B according to the Cochrane Collaboration handbook, rated by two observers.	DMPs significantly enhance the quality of care for depression. Costs are within the range of other widely accepted public health improvements.
Vergouwen et al, 2003	Descriptive review; N=19 (19 RCTs).	Collaborative care defined as a systematic approach that improves patient education and with an active	To be included in the review, studies had to be: English language, peer-reviewed journals; addressing interventions aimed	Studies on interventions that did not target the patient directly were	Educational interventions failed to demonstrate a clear benefit on adherence and depression outcome. Collaborative

Study	Design / N	Intervention	Inclusion criteria	Exclusion criteria	Results / Conclusions
al, 2003	N=19 (19 RCTs).	role of mental health professionals or other care extenders, such as nurses, in primary care; collaborative interventions are multimodal i.e. affecting patient and physician as well as the system of care. Studies were classified into 2 broad categories of treatment modality: patient education and collaborative care.	at improving adherence to prescribed antidepressant medication in patients with unipolar depression.	excluded.	care interventions tested in primary care demonstrated significant improvements in the adherence during the acute and continuation phase of treatment and were associated with clinical benefit especially in patients suffering from major depression who were prescribed adequate dosages of antidepressants.
Christensen et al, 2008	Descriptive review; N=55 (55 RCTs/ CCTs).	Interventions coded according to 4 different systems: components of care, treatment type, primary intention or aim of the study and detailed components.	Included were RCTs and CCTs that measured at least one outcome measure of depression and a control group of either treatment as usual or waitlist control.	Non-English articles on studies involving quality and safety issues, side effects, comorbidity or adolescent population were excluded.	Review of professional roles was associated with improved outcome OR 3.8 (95% CI 1.08-14.51); systematic tracking of patients (other than doctor) was associated with improved depression outcome; monitoring and delivery of treatment was best done by health professionals with a mental health background or by practice nurses rather than by pharmacists; there is a significant association between patient preferences and positive depression outcomes; training of GPs in depression care and provision of clinical practice guidelines were not associated significantly with improved outcomes.
Badamgarav et al, 2003	Meta-analysis; N=19 (17 RCTs, 1 study with quasi-experimental design (controlled before and after), 1 study including results from a RCT and a quasi-experimental controlled trial).	Disease management; interventions designed to manage or prevent a chronic condition by using a systematic approach to care and potentially employing multiple treatment modalities; systematic approach to care (or guideline) defined as a set of systematically developed statements to assist practitioner's and patients' decisions about appropiate health care for a specific clinical circumstance. Outcomes are potentially effected	To be included in the review, studies had to be: RCTs; English-language articles evaluating the effectiveness of DMPs in improving care or reducing costs for patients with depression.	Excluded were: programmes exclusively evaluating single treatment modalities (e.g. psychotherapy or specific pharmacological agents); reporting only pediatric cases; reviews, case reports, editorials, letters or abstracts of meeting presentations and	Disease management appears to improve the detection and care of patients with depression. Further research is needed to assess the cost-effectiveness and consideration should be given to implementation of these programmes.

	Design	Intervention / Description	Inclusion criteria	Exclusion criteria	Conclusions
		by both practitioners' adherence to guidelines and patients' compliance.		articles not using an acceptable experimental or quasi-experimental study design; articles not reporting sufficient information to allow for estimation of at least one measure of a program effect of interest and its variance.	
Gensichen et al, 2006	Meta-analysis; N=13 (13 RCTs).	Case management taking responsibility for following-up patients determining whether patients were continuing the prescribed treatment as intended, assessing whether depressive symptoms were improving, and taking action when patients were not adhering to guideline-based treatment or when they are not showing expected improvement. Case managent consists of five essential components: identification of patients in need of services; assessment of the individual patient's needs; developing a treatment plan; coordination of care; monitoring outcomes and altering care when favourable outcomes are not achieved.	Included were RCTs that address: major depression or depressive episode based on DSM-IV or ICD-10 criteria diagnosed by a valid instrument; case management as an intervention for continuity for care including at least the systematic monitoring of symptoms; follow-up for 6-12 months; interventions located in community-based care; severity of depression symptoms as principal outcomes measured by validated instruments and a change of the patients' adherence to drug treatment.	Excluded were studies with: incomplete study information available; low methodological quality; focus on action on doctors, patients' relatives, inpatients, drug-users, homeless people, disabled people, or depression in specific circumstances such as end-of-life or pregnancy. Also excluded were studies on specific interventions for primary prevention, screening, diagnosis, case finding, health education, pharmacotherapy, counselling, psychotherapy, social work and intensive support.	Case management is an effective intervention to improve management of major depression in primary health care. It provides an additional benefit to drug therapy. The mechanism of action of case management may be through increased medication adherence. Complex case management is not recommended over standard case management considering the higher costs and preliminary results of the subgroup analysis. Further studies are required on complexity and cost effectiveness of case management.
Gilbody et al, 2006, Br J Psychiatry	Descriptive review; N=11 (11 RCTs).	Methods of organising and delivering enhanced primary health care for depression, including clinical educative strategies, clinical practice guidelines	Included in the review were full economic evaluations (cost-benefit analyses, cost-effectiveness analyses, cost-minimisation analyses or cost-utility analyses) based	Studies examining the effectiveness of psychotherapy or drug therapy alone were not	Enhancements of care (collaborative care, case management) mostly produce improved outcomes but are associated with increased direct health care costs

Reference	Design	Intervention / focus	Inclusion / exclusion	Results / Conclusions
		(implementation), collaborative care (involving an enhanced case management role for nonmedical specialists such as practice nurses and integrated working relationships between primary care and specialist/secondary services) and stepped care.	included.	over the short term. Educational strategies did not lead to improved clinical outcomes and were associated with increased costs.
		upon robust randomised epidemiological designs that examined the cost-effectiveness of organisational interventions to improve quality and outcome of care for depression in primary care settings. These organisational interventions include: clinical education; dissemination and implementation of treatment or management guidelines; reconfiguration of roles within primary care; case management or active follow-up; consultation-liason or other methods of improving working relationships between primary care and specialist/secondary services.		
Gilbody et al, 2003	Descriptive review; N=36 (29 RCTs/ CCTs, 5 pre-post studies, 2 interrupted time-series studies).	Enhanced primary care for depression; (organizing and delivering) intensive organisational strategies such as case management and stepped care. Collaborative care involves an enhanced case management role for nonmedical specialists such as practice nurses and integrated working relationships between primary care and specialist/secondary services.	To be included in the review, studies had to be: evaluations by RCT, CCT, controlled before/and/after studies and interrupted time/series study design examining the effectiveness of an organisational or educational intervention targeted at primary health care professionals and patients or novel models of providing health care.	Studies examining only the efficacy of patient-level interventions or the effectiveness of screening strategies were excluded.	Improved outcomes through DMPs using a collaborative care/case management approach can be expected but are associated with increased cost (increased primary care visits, increased use of antidepressant medication, access to secondary care) and will require investment. Educational strategies did not lead to improved clinical outcomes and were associated with increased costs; these have minimal impact on clinical outcomes unless they are supported by enhancements of care.
Pirraglia et al, 2004	Descriptive review; N=9 (9 RCTs).	Optimal management of depression in primary care. Classification of Wagner et al. was applied with the categories: explicit plans and protocols, such as guidelines; changes in delivery system design; attention to the information needs of patients; ready access to necessary expertise; information support systems.	This review was part of a larger project to systematically review cost-utility analyses in medicine; selection methods were published elsewhere.	See Inclusion criteria.	Effective strategies are: collaborative care; stepped collaborative care; quality improvement; case management; pharmacist-provided prescribing information and patient education; guideline implementation strategies embedded in complex interventions. Strategies not shown to be effective: guidelines and educational strategies, other interventions. Strategies effective in improving

					patient outcome generally were those with complex interventions incorporating clinical education, an enhanced role for the nurse (nurse case management) and a greater degree of integration between primary and secondary care (consultation-liaison). Telephone medication counseling delivered by practice nurses or trained counselors was also effective. Simple guideline implementation and educational strategies were generally ineffective. Succesful strategies integrate education with other organizational approaches and are multifaceted. Evidence suggests a differential clinical effectiveness and cost-effectiveness of nurse case management, collaborative care and quality improvement according to severity of illness. Further research is needed to establish who should deliver enhanced care, who should receive it, and for how long.
Williams et al., 2007	Descriptive review; N=28 (28 RCTs).	Examination of cost-utility of depression management is relevant, particularly of the marked impact of the disorder on quality of life.	To be included in the review, studies had to be RCTs published in English language meeting the following criteria: samples comprising adult patients with a depressive disorder who were cared for in a primary care setting. Interventions needed to augment usual care by incorporating at least one patient-directed element from the Chronic Care Model (eg. patient self-management, active follow-up); reporting clinically meaningful outcomes, such as change in depressive symptoms. Interventions directed solely at the clinician or health care system were not included.	Not specified.	Pharmacological interventions generally had lower costs per QALY than nonpharmacological interventions. Psychotherapy alone, care management alone and psychotherapy plus care management alone all had lower costs per QALY than usual care. Depression screening and treatment appeared to fall within the cost-utility ranges accepted for common nonpsychiatric medical conditions. Paucity of literature on cost-utility analysis of depression management is noticed. Novel strategies for depression such as self-help strategies and stepped

behavioural models are areas to which cost-utility analysis might be extended.

RCT: randomised controlled trial; CCT: controlled clinical trial; DMP disease management programme

Study	Inclusion	Exclusion	Population (N, mean age, % male, severity, setting)	Intervention	Components (SMS, DSD, CIS, DS)*	Follow-up (months)	Quality study design
Adler et al, 2004	Patients that 1) received care from a primary care practice, 2) met DSM-IV criteria for major depression and/or dysthymia, 3) are ≥18 years, 4) could read and understand English, 5) had no acute life threatening disease, 6) were not pregnant (or giving birth ≤6 weeks ago).	Patients with current alcoholism, current bipolar disorder, current psychotic disorders.	N=507; I=42.9 (13.8), C=41.7 (14.0); I=30.6, C=25.7; total 40% met criteria for major depression, 24% for dysthymia and 36% for double depression (DD); 9 primary care practices in metropolitan Boston; 5 general medical practices at an academic medical center, 1 urban and 2 suburban community Boston medical practices, and a community health center.	The intervention was guided by the use of a protocol based on clinical pharmacy principles and AHCPR guidelines, and did not involve prescribing a specific AD medication. The protocol emphasized: 1) obtaining a thorough medication history, 2) assessing a patient's medication regimen for drug-related problems (such as side effects or drug interactions), 3) monitoring drug efficacy and toxicity, especially for the symptoms of depression, 4) educating patients about depression and antidepressants, 5) encouraging patients to start and maintain AD therapy, and 6) facilitating communication with a patient's PCP.	SMS, DSD, CIS, DS	6	70
Araya et al, 2003	Low-income women with major depression (DSM-IV).	Patients with serious suicidal risk, current psychotic symptoms, history of mania, current alcohol abuse, patients who had a psychiatric consult or admission in the 3 months before the interview.	N=240; I=43.0 (12.8); I=0; Ham-D/ HDRS I=19.8 (3.4) C=19.7 (4.0); 3 primary care clinics in deprived urban areas of Santiago, Chile, representive of Santiago in terms of resources and clinical and sociodemographic characteristics of patients.	Stepped care improvement programme with a structured psychoeducational group, systematic monitoring of clinical progress and a structured pharmacotherapy programme for patients with severe or persistent depression.	SMS, DSD, CIS, DS	6	80
Arthur et al, 2002	Older people (75+) scoring 5 or more on the 15-item Geriatric Depression Scale (GDS-15).	Not specified.	N=93; I=30, C=17; I=82 (iq 78-87), C=79 (iq 76-81) median scores; GDS15 I=8 (iq 6-9), C=6.5 (iq 6-8); single large general practice in Leicestershire.	Routine follow-up mental health assessment by a specialist Community Mental Health Team (CMHT) for older people with depressive symptoms identified by practice nurses at a health check for people over the age of 75 years. The CMHT aims to see the patient within	DSD, CIS	18	60

Study	Inclusion criteria	Exclusion criteria	Population	Intervention	Components		
				3 weeks of referral to carry out a full mental history, review current medication needs in relation to mental health problems, and assess the likely impact of further CMHT interventions.			
Aubert et al, 2003	Patients with a new prescription for an AD and no prescription history for AD during the previous 180 days.	Not specified.	N=4249 (minimal intervention group not included); I=29, C=30; I= 54 (16), C=54 (16); NR; Home care offered by employer.	Telephone counselling by a psychiatric nurse (4x) and education materials by e-mail (6x) on medication adherence during a 8 month period following AHCPR guidelines for the clinical management of depression.	SMS, DSD	7	50
Blanchard et al, 1999	Patients screened by Diagnostic Depression Scale (DPDS) as depressed in 1988 and 1990 or only in 1990.	Not specified.	N=64; Total: 76 (SD 6,8); Total: 15%; DPDS Total=8,43 (2,4); Gospel Oak, North London, primary care.	Research nurse visiting patients at home and implementing management plans.	SMS, DSD	14,5	65
Brown et al, 2000; CQI	Patients with a Hopkins Symptom Checklist depression scale score (HSCL-D>1,1) that used an eligible PCP and remained in a HMO, returned a follow-up questionnaire and retained with same PCP throughout follow-up.	Not specified.	Primary Care Practices (PCPs); N=160, Patients: N=928; PCP: I=42.7, C=42.2 Patients: I=53.0, C=54.6; PCP: I=72.6 C=78.9. Patients: I=21.9, C=25.7; HSCL-D I=1,44, C=1,48; HMO Kaiser Permanente North West Division, primary care.	Continuous quality improvement (CQI) to implement a guideline on depression treatment. The guideline implemented was a compact and locally relevant version of the AHCPR guidelines.	SMS, DSD, DS	12	60
Brown et al, 2000; AD	See Brown et al, 2000; CQI	Not specified.	Primary Care Practices (PCPs); N=160, Patients: N=928; PCP: I=43.8, C=41.2, Patients: I=54.3, C=53.2; PCPs: I=75.9, C=75.3, Patients: I=24.1, C=23.3; HSCL-D I=1,48, C=1,44; HMO Kaiser Permanente North West Division, primary care.	Academic detailing to implement a guideline on depression treatment.	DSD, DS	12	75
Bruce et	Patients 60 years or	Patients with CES-D≤20.	N=598; age≥ 75 years	POSPECT intervention: 2 major	DSD, CIS, DS	12	75

Study	Inclusion criteria	Exclusion criteria	Sample characteristics	Intervention	Components	Duration	%
al, 2004	older, able to give informed consent, with a MMSE score ≥18, that communicate in English and have a CES-D>20.		in I=31.9%, C=29.5% (no mean age is given); I=30.9, C=25.5; Ham-D I=18.6 (6.1), C=17.5 (5.8); 20 primary care practices.	components: 1) physician knowledge, addressed by a clinical algorithm and 2) treatment management, operationalised by depression care managers.	SMS, DSD	12	65
Capocci a et al, 2004	Patients diagnosed with a new episode of depression according to the PRIME-MD that started on AD medication.	Patients 1) under 18 years, 2) with terminal illness, 3) with psychosis, 4) with recent (within 3 months) alcohol or substance abuse, 5) with two or more suicide attempts, 6) pregnant or nursing, 7) with limited command of English language, 8) with unwillingness to use the primary care centre as source of care the next 12 months.	N=74; I=38.2 (13.8), C=39.4 (13.4); I=17, C=30; Mean HSCL-20 I=1.83 (0.10), C=1.75 (0.10); SCID major depression I= 53%, C=28%; primary care clinic in an academic environment.	Enhanced care consisting of a pharmacist collaborating with primary care providers to facilitate patient education, the initiation and adjustment of AD dosages, the monitoring of patient adherence to the treatment regimen, management of adverse reactions, and prevention of relapse. Additional follow-up by a clinical pharmacist, weekly telephone calls the first 4 weeks, then calls every 2 weeks through week 12, and then during month 4-12 calls every other month; also patients were recommended to visit the primary care provider in week 4 and 12; appointments with mental health providers were facilitated.			
Ciechan owkski et al, 2004	Adults of 60 years or older receiving services from senior service agencies or living in senior public housing, having a diagnosis of DSM-IV minor depression or dysthymia.	Adults with 1) a score of less than 3 out 6 points to questions from the MMSE, 2) DSM-IV major depression.	N=138; I=72.6 (8.4), C=73.5 (8.5); I=18, C=24; HSCL-20 I=1.3 (0.5), C=1.2 (0.5); Senior service agencies or senior public housing.	Home based intervention focusing on problem solving therapy.	SMS, DSD, CIS	12	80
Cuijpers et al, 2001	Inhabitants of residential homes.	Inhabitants with MMSE score <17.	N=424; NR; I=25.1, C=17.8; GDS I=15.86 (3.99), C=15.49 (3.63); 10 residential homes in various parts of the Netherlands.	Depression prevention programme with education and feedback for caregivers and education and group interventions for inhabitants of residential homes.	SMS, CIS	12	70
Datto et al, 2003	Patients with a CES-D≥16.	Patients with a significant suicidal risk, ongoing substance abuse problems, current psychotic symptoms, evidence for bipolar affective disorder.	N=61; I=44.6 (16.9), C=49.2 (16.5); I=33.3, C=45.2; CES-D I=32.8 (10.5), C=31.6 (10.0); percentage diagnosed with MDD (MINI) I=86.2, C=83.3; 35 primary care practices in the University of Pennsylvania Health System.	Telephone disease management: maintain focus on mental health given many competing problems, assistance with referral to mental health as needed, interval outcome monitoring and provider feedback.	DSD, CIS, DS	4	65

Study						
Dietrich et al, 2004	Patients that have a telephone, speak English, met DSM-IV criteria for major depression and/or dysthymia, are ≥18 years, have a HSCL-20 of at least 0.5 6, and are starting or changing treatment for depression.	Patients 1) unobtainable for an evaluation interview within 14 days of their index primary care visit, 2) pregnant, 3) with suicidal thoughts, 4) with schizophrenia, 5) with bipolar disorder, 6) with PTSD, 7) with substance misuse disorder.	N=405; I=41.8 (14,1), C=42.2 (15.3); I=16.5, C=23.8; HSCL-20 I=2.03 (0.65), C=1.98 (0.65); 5 health care organisations in the USA and affiliated primary care practices.	Care manager that supports patients by telephone and reports to clinicians. The case manager is supervised and advised by a psychiatrist.	SMS, DSD, CIS, DS	6	75
Dobscha et al, 2006	Patients with PHQ-9 depression scores of 10 to 25 or HSCL-20 scores ≥1.0, repeatedly.	Patients 1) not reached by telephone, 2) with concerns about safety or confusion, 3) with active suicide ideation, 4) with possible dementia.	N=375; I=57.3 (10,9), C=56.3 (11.2); I=93, C=93; HSCL-20 I=1.9 (0.57), C=1.9 (0.50); 5 primary care clinics of 1 Veterans Affairs medical center.	Depression decision support with a decision support care manager and a decision support team to educate patients to enhance self management and to help clinicians to treat depression adequately by providing them with feedback and recommendations on PHQ-9 scores and depression progress in patients.	SMS, DSD, CIS, DS	12	85
Finley et al, 2003	Patients starting AD for the expressed purpose of treating depressive symptoms.	Patients with 1) evidence of taking AD in the preceding 6 months, 2) current symptoms of mania or bipolar disorder, 3) concurrent psychiatric or psychological treatment, 4) psychotic symptoms or eminent suicidality, 5) active substance abuse or dependence, 6) referral to HMOs psychiatric department.	N=125; I=54.4 (14,1), C=54.1 (17.3); I=15, C=16; BIDS I=18.7 (5,8), C=18.3 (5,8); HMO Kaiser Permanente medical center in San Rafael California with 30 primary care providers.	Collaborative care model: clinical pharmacists providing drug therapy management and treatment follow-up to patients with depression by clinical appointments and telephone calls, if changes to the AD regime were warranted the pharmacist communicated this recommendation to the provider by telephone call or by mail. Also a psychiatrist was available for consultation for the pharmacist and for a 1 hour meeting each week.	SMS, DSD, CIS, DS	6	70
Flaherty et al, 1998	Patients 1) with GDS≥10, 2) 65 years or older, 3) closed to home care services because patient goals were met or because of hospitalisation.	Patients 1) younger than 65, 2) still receiving (or open to) home care services or that had been closed to home care because of death, 3) with direct nursing home admission, 4) with changes in HCAs or 5) that moved out of the catchment area.	N=150; I=81(7,3), C=77(7.1); I=33, C=36; NR; Home Care by the nonprofit Visiting Nurse Association in St. Louis.	Total Quality Management (TQM): a new model of care, consideration for what staff thinks what can and can't be done in a practical way; use of a screening tool for depression (GDS) to identify depressed patients; educational seminar for home care staff, algorithm for the treatment of depression based on the GDS score, including a pharmacotherapeutical algorithm.	DSD, CIS, DS	12	60
Fortney et al, 2007	Patients with PHQ-9 ≥12, with PCPs feeling comfortable to treat.	Patients with 1) schizophrenia, 2) current suicide ideation, 3) recent bereavement, 4) pregnancy, 5) a court-	N=395; I=58.4 (12,2), C=59.8 (12.1); I=93,8, C=89,9; HSCL-20 I=1.9 (0.7), C=1.8 (0.7); Veterans Integrated	Telemedicine Enhanced Antidepressant Management (TEAM): Stepped care model of depression treatment. Treatment level was increased for patients	SMS, DSD, CIS, DS	12	70

Study	Inclusion / Exclusion criteria	Setting / N	Intervention	Measures		
	appointed guardian, 6) substance dependence, 7) bipolar disorder, 8) cognitive impairment, 9) special mental health treatment.	Service Networks, 7 community based outpatient clinics in rural areas, primary care.	failing to respond to lower levels of care by involving a greater number of intervention personnel with increasing mental health expertise.			
Goldberg et al, 1998; AD	Patients 8 to 75 years that are known depressives. Patients that are 1) non-competent, 2) non English speaking, 3) without current address or phone number.	N=1497; Providers: I=40.2, C=37.2, Patients: NR; NR; Providers: I=55.6, C=60.9, Patients: NR; 4 primary care clinic sites consisting of several small group practices; 2 clinics are staff model HMOs, 2 clinics are associated with the university.	Academic detailing to implement a guideline on depression treatment.	CIS, DS	12	60
Goldberg et al, 1998; CQI	See Goldberg et al, 1998; AD. See Goldberg et al, 1998; AD.	N=1490; Providers: I=38.2, C=37.2, Patients: NR; Providers: I=51.4, C=60.9, Patients: NR; NR; 4 primary care clinic sites consisting of several small group practices; 2 clinics are staff model HMOs, 2 clinics are associated with the university.	Academic detailing to implement a guideline on depression treatment and Continuous quality improvement (CQI).	DSD, CIS, DS	12	55
Hedrick et al, 2003	Patients with a major depressive episode and/ or dysthymia. Patients 1) recently visiting a mental health clinic or having a future appointment, 2) requiring treatment for substance abuse or PTSD, 3) with acute suicidality, 4) with psychosis, 5) with another condition requiring immediate treatment.	N=354; I=57.8 (13.5), C=56.6 (14.2); I=95.2, C=95.7; HSCL-20 I=1.96 (0.65), C=1.83 (0.70); VA primary care clinic.	Collaborative care: a mental health team provided a treatment plan to the PCP, telephoned patients to support adherence to the plan, reviewed treatment results and suggested modifications to the provider. Stepped care was given.	SMS, DSD, CIS, DS	9	65
Hunkeler et al, 2000	Patients with major depressive disorder or dysthymia and a prescription for SSRI (fluoxetine hydrochloride or paroxetine). Patients that 1) received an AD prescription in the past 6 months, 2) inadequate command of the English language, 3) reported current problems with substance abuse, current suicide risk or thoughts of violence.	N=302; Total: 55.4; I=28, C=34; Ham-D I=16.6 (6.2), C=17.4 (6.6); Hayward and San Francisco primary care clinics within Kaiser Permanente Northern California.	Nurse telehealth care and peer support.	SMS, DSD, CIS	6	65

Study	Inclusion criteria	Sample	Intervention	Categories		
Jarjoura et al, 2004	Patients 1) 18 years or older, 2) screened positive for a major depression episode according to the PRIME-MD, 3) that were not receiving intervention for mental health problems or were not seeking help for depression or other emotional problems, 4) that gave informed consent, 5) that respond to symptom questions, 6) are enrolled in Medicaid or are below the poverty line.	N=61; I=45 (SE 2), C=46 (SE 2); I=24, C=39; BDI I=28 (2) C=23 (2); NR; Internal Medicine Residency Clinic a primary care and NOVA, a local public mental health agency, Ohio. Patients with suicide ideation.	For the intervention group patients, a screening nurse advised residents regarding the positive depression screen, handed them a standardized protocol outline, and attempted to arrange behavioural care. Resident physicians were taught to educate the patients about their depression, to convince them about the benefits of behavioural health care, and advised them to make appointments at the local public mental health agency (NOVA), following AHCPR guidelines.	SMS, DSD, CIS, DS	12	70
Katon et al, 1995, Lin et al, 1999; Major depression	Patients with 1) SCL-20 ≥ 0.75, 2) age 18-80 years, 3) willingness to take AD.	N=91; I=43.2 (15.4), C=42.3 (12.7); I=22.5, C=11.9; HSCL-90 I=2.35 (0.49), C=2.23 (0.48); primary care.	Patients with 1) current alcohol abuse, 2) current psychotic symptoms or suicide ideation, 3) dementia, 4) pregnancy, 5) terminal illness, 6) limited command of English, 7) the plan to withdraw from the Group Health Insurance Plan in next 12 months. Intervention patients received increased intensity and frequency of visits over the first 4 to 6 weeks of treatment (visits 1 and 3 with a primary care physician, visits 2 and 4 with a psychiatrist) and continued surveillance of adherence to medication regimens during the continuation and maintenance phases of treatment. Patient education in these visits was supplemented by videotaped and written materials.	SMS, DSD, CIS, DS	7	60
Katon et al, 1996, Lin et al, 1999; Major depression	Patients with 1) SCL-20 ≥ 0.75, 2) age 18-80 years, 3) willingness to take AD, 4) major depression (DSM-III).	N=65; I=43.1 (9.3), C=44.8 (15.9); I=22.6, C=26.5; HSCL-20 I=2.46 (0.53), C=2.35 (0.51); large primary care clinic in western Washington (HMO).	Patients with 1) current alcohol abuse, 2) current psychotic symptoms or suicide ideation, 3) dementia, 4) pregnancy, 5) terminal illness, 6) limited command of English, 7) the plan to withdraw from the Group Health Insurance Plan in next 12 months. A multifaceted intervention: behavioural treatment to increase adaptive coping strategies and counselling to improve medication adherence; visits and telephone contacts with psychologists; psychologists give feedback to primary care physicians; psychiatrist gives feedback to psychologists.	SMS, DSD, CIS, DS	7	70
Katon et al, 2001	Patients 1) 18-80 years, 2) with a new AD prescription (not having one 120 days prior), 3) with depression according to the SCID, 4) with high …	N=386; I=46.4 (11.9), C=45.6 (13.3); I=24.6, C=28.1; HSCL-20 I=0.83 (0.39), C=0.84 (0.35); 4 primary care clinics in western Washington. Patients 1) with current alcohol abuse 2) being pregnant or currently nursing, 3) with the plan to withdraw from the Group Health Cooperative in the next 12 months, 4) …	A multifaceted intervention: 2 primary care visits with a depression specialist and 3 telephone visits over a 1-year period aimed at enhancing adherence to antidepressant medication; recognition of prodromal symptoms, monitoring of symptoms, …	SMS, DSD, CIS, DS	12	80

Author, year	Inclusion criteria	Population	Intervention			
	currently seeing a psychiatrist, 5) with limited command of the English language, 6) recently using lithium or antipsychotic medication.	–	and development of a written relapse prevention plan.		28	75
	epidemiologic risk of relapse or 4 or more residual major depressive symptoms but with a mean HSCL<1.0 and a history of major depression/ dysthymia, or 5) fewer than 4 symptoms of major depressive symptoms and a history of 3 or more episodes of major depression/ dysthymia.					
Katon et al, 2002, Lin et al, 2000; Moderate severity	Patients 1) 18-80 years 2) with a new AD prescription (not having one 120 days prior), 3) 4 or more residual major depressive symptoms or having recurrent depression (2 or more prior episodes) or dysthymia, 4) 4 or more DSM-IV major depressive symptoms on the SCID and a mean score on the HSCL-20 ≥1.0, or 5) fewer than 4 symptoms major depressive symptoms but with HSCL-20 ≥1.5; moderate severity= (HSCL-20 score between 1.0 and 2.0).	N=228; I=47.2 (14.0), C=46.7 (13.4); I=32.5, C=18.4; moderate severity (HSCL-20 between 1.0 and 2.0); 4 primary care clinics in western Washington (HMO).	A multifaceted intervention (stepped collaborative care): 2 primary care visits with a psychiatrist and a telephone call in between, additional visits if necessary. The psychiatrist tracks progress of patients and helps with adjustment of medication when necessary.	SMS, DSD, CIS, DS	28	75
Katzelnick et al, 2000	Patients 1) between 25-63 years, 2) with continuous enrolment for the last 2 years, 3) with ambulatory visits count above the 85th percentile for both of the previous 2 years (high utilizers), 4) screening positive for either current major depression or major depression in partial remission on the SCID 5), with an Ham-D score ≥15.	N=407; I=45.6 (95% CI 44.0-47.1), C=45.4 (95% CI 43.9-46.9); I=23.4, C=21.7; Ham-D I=19.1 (18.7-19.6), C=19.2 (18.7-19.7); 163 primary care practices in 3 HMOs located in different geographic regions of the USA.	The DMP included patient education materials, physician education programmes, telephone-based treatment coordination, and antidepressant pharmacotherapy initiated and managed by patients' primary care physicians.	SMS, DSD, CIS, DS	12	85

Patients with 1) recent treatment for alcohol abuse or other substance abuse, 2) past treatment for schizophrenia or bipolar disorder, 3) life-threatening medical disorders, 4) active treatment for depression, 5) Ham-D score <15, 6) contra-indications to taking AD, 7) treatment by a psychiatrist within the past 4 months, 8) pregnancy or breastfeeding, 9) planned

Patients 1) with current alcohol abuse 2) being pregnant or currently nursing, 3) with the plan to withdraw from the Group Health Cooperative in the next 12 months, 4) currently seeing a psychiatrist, 5) with limited command of the English language, 6) recently using lithium or antipsychotic medication.

	pregnancy within the next year, 10) positive screen for alcohol abuse, 11) intent to disenroll from the HMO.					
Llewellyn -Jones et al, 1999	English speaking residents aged 65 or over and cognitively able to provide accurate information -memory-orientation- concentration error score less than 20) were screened for depression. Inclusion criteria: GDS ≥10) and absence of pronounced cognitive impairment (mini mental state examination score ≥18).	Patients with severe physical illness or current treatment from a mental health professional for depression or serious mental illness.	N=220 (169 completers) taken care for by 34 GPs; I=84.9 (5.9), C=83.8 (5.7); Patients: I=17, C=14, GPs: 76%; Baseline GDS I=13.5 (3.2), C=13.5 (3.4); Large residential facility in Sydney, population living in self care units and hospitals.	Shared care intervention including: a) multidisciplinary consultation and collaboration (removing barriers to care); b) training of GPs and carers in detection and management of depression (carer education), c) depression related health education and activity programmes for residents (health education and health promotion).	SMS, DSD, DS	9,5	70
Mann et al, 1998; Study 2	Patients aged 18-74 years, who had been depressed for at least four weeks, recruited from routine general practice (attenders currently receiving treatment from their GP for depression or presenting with a new episode were included).	Patients with suicidal ideation, depression representing a phase in a manic-depressive psychosis, or currently receiving treatment for depression from specialist psychiatric services.	N=419; Women: 43.1 (15.3), Men: 48.3 (13.7); N=22; Altogether, 89% scored at or above a cut-point of 10 on the BDI, indicating the presence of at least mild depression, 52% scored 20 or more, indicating at least moderate levels of depression, and 16% scored 30 or more, indicating severe depression, 82% reported symptoms that met criteria for DSM-III major depression with NAI assessment (Nurse Assessment Interview); 19 general practices participating in the Medical Research Council General Practice Research Framework, distributed throughout England (many with a rural location) (5-47 patients per practice).	Intervention group: the nurse worked to a specially devised manual and was advised to see the patient regularly during the first month, but with no specific regime thereafter. A total contact time of eight hours per patient over four months was recommended, including initial and final assessments. Patients could see the GP at any time at their own, the GP's, or the nurse's request. The nurse could discuss a patient with the GP at any time, all such contacts being recorded. At each follow-up visit, the nurse recorded the content of her interview, categorizing according to the headings: monitoring change in mental state, encouraging compliance, providing education, or facilitating a social intervention.	DSD, CIS	4	80

Study	Population	Exclusion	Sample	Intervention	Measures		
Miranda et al, 2003; AD	Low-income (working) young minority women with positive screen for current major depression and a negative score for mania, psychosis, or past month alcohol or drug abuse or dependence.	Women with bereavement, positive for current alcohol or drug problems, being pregnant or planning to become pregnant within the next 6 months, currently breastfeeding, or currently receiving mental health care.	N=177; I =28.7 (6.6), C= 29.5 (9.1); I=0, C=0; Current major depression; Washington, DC, suburban area in county-run Women, Infants, and Children food subsidy programs and Title X family planning clinics.	Education meetings; Medication; CBT; Community care. Medication: primary care nurse practitioners supervised by psychiatrist. Duration 6 months, in line with Agency for Healthcare Research and Quality (AHRQ) guidelines for the acute and maintenance phases of depression treatment. Adjustments in dosage were based on changes in Hamilton Depression Rating Scale scores and adequate time for medication effect. Clinicians also assessed participants at face-to-face meetings by using the Clinical Global Impression Scale. When adverse effects occurred or if by the ninth week, the patient did not show a significant clinical response despite dose adjustments, buproprion, an antidepressant with a different presumed mechanism of action as well as a different adverse effect profile, was administered. Participants treated with medications were observed in person every 2 weeks until a stable dose was achieved, and then every 4 weeks thereafter. The nurses scheduled weekly telephone calls to assess adverse effects, adherence, and treatment effects. Improvement was assessed by using the HDRS and Beck Depression Inventory. If after 8 weeks of treatment a participant's scores were still elevated, an additional 8-week treatment was offered. Referral to Community Care: Women assigned to community referral as usual were educated about depression and mental health treatments available in the community. Referred participants were contacted to encourage them to attend the intake appointment for care.	SMS, DSD, CIS, DS	6	75
Miranda et al, 2003; CBT	See Miranda et al, 2003; AD.	See Miranda et al, 2003; AD.	N=179, I =29.8 (7.9), C =29.5 (9.1); I=0, C=0; Current major depression; Washington, DC, suburban area in county-run Women,	Education meetings; Medication; CBT; Community care. Cognitive Behavioural Therapy; Women assigned to the psychotherapy intervention were treated by experienced psychotherapists supervised by a licensed clinical	SMS, DSD, CIS, DS	6	75

| | | | | | SMS, DSD | 4 | 60 |

psychologist in 8 weekly sessions, either in group or individually, depending on feasibility of women attending group. Participants were each given a CBT manual that they kept after treatment was concluded. The therapy protocol involved homework and daily monitoring, with a focus on cognitive management of mood, engaging in pleasant activities, and improving relationships with others. Improvement was assessed by using the HDRS and Beck Depression Inventory. If after 8 weeks of treatment a participant's scores were still elevated, an additional 8-week treatment was offered. Referral to Community Care: Women assigned to community referral as usual were educated about depression and mental health treatments available in the community. Referred participants were contacted to encourage them to attend the intake appointment for care.

Infants, and Children food subsidy programs and Title X family planning clinics.

Oslin et al, 2003

Subjects aged 18 and older; screened positively on the CES-D (total score >15), indicated suicidal/death ideation or who reported consumption of eight or more drinks in the previous week were invited to receive a further baseline evaluation for potential inclusion in the randomized trial. Further inclusion criterion was: demonstrating signs and symptoms of a depressive disorder (major depression, dysthymia, or persistent minor depression).

Patients already in mental health (or substance abuse care) for the condition that they screened positively for and those with a Brief Orientation Memory, Concentration test (BOMC) more than 16 were excluded from further assessment. Further exclusion criteria were active suicidal ideation, regular use of illicit substances, current hallucinations and delusions or a history of a primary psychotic disorder, a history of mania or hypomania, and having a high potential for alcohol withdrawal symptoms as indicated by a score more than 14 on the Alcohol Dependence Scale (ADS).

N=97 (incl. at-risk drinkers) (37 clinicians). Depression cases only: N=77, I=61.3 (10,3), C=61.9 (11,3); I= 95.7, C=96.1; Among those with a depressive disorder, 53 (68.8%) had major depression, no differences in the distribution of types of depression (major, minor, or dysthymia) between usual care and TDM; Urban VA medical center.

Telephone-based Disease Management (TDM) programme consisting of regular contacts with each subject by a behavioural health specialist (BHS) to assist in assessment, education, support, and treatment planning. The BHS maintained regularly scheduled telephone contact to develop a treatment plan, to monitor treatment effectiveness and adverse effects, assess and encourage treatment adherence, and offer support and education. Calls were scheduled at 1, 3, 6, 9, 12, 18, and 24 weeks after the initial clinical assessment. The depression manual followed closely the disease management approach developed by Mulsant and colleagues. Initial focus of the interaction between patients and BHS was to address issues of stigma and focused on engaging the patient in treatment. In cases in which an antidepressant was clinically indicated, patients were

Scale (ADS).

clinically indicated, patients were typically started on a serotonin selective reuptake inhibitor (SSRI). In addition to behavioural health specific recommendations, the BHS assessed for medical complications of depression and alcohol use and may make recommendations for further medical management to assist in differential diagnosis or management. Each clinical contact lasted approximately 45 minutes, with the first 30 minutes focused on evaluation of symptoms and adherence to the treatment plan. The remaining time was used to motivate patients to adhere to the treatment plan and to provide education about the illness or treatments. In addition to the training and the manuals, the BHSs met weekly with a psychiatrist to review each treatment plan. The treatment plan included both pharmacological management of depression and psychosocial support. Following the VA and AHRQ treatment guidelines, particular attention was placed on assessments at 6 weeks, with recommendations to reevaluate the treatment plan for those who are unchanged or worse, to intensify or enhance treatment for those with partial responses (defined as more than a 30% decrease in depressive symptoms without meeting remission criteria (HDRS score≤10), and to continue treatment for those with significant improvements. Attention also focused on assessments at 12 weeks with recommendations for reevaluating treatment for those with residual symptoms and to continue treatment for those in remission.

			SMS, DSD	3	70
Peveler et al, 1999; Leaflet + drug counselling	Patients with a clinical diagnosis of depressive illness.	Patients receiving drug within 3 months, having a contra-indication (allergy, heart disease, glaucoma, pregnancy), or receiving incompatible drugs, and patients with high suicide	Randomised: N=213. Full 12 week data: N=190; Total: 47.4 (23-72); Total: 26; Total: 49% MDD in past month, HADS score 10.2 (SD 4.3); GPs in	Information leaflet containing information about the drug, unwanted effects, and what to do in the event of missing a dose. Patients were given drug counselling by a nurse at weeks 2 and 8, according to a written protocol. Sessions	

	risk.	Wessex (Primary care).	included assessment of daily routine and lifestyle, attitudes to treatment and understanding of the reasons for treatment, education about depressive illness and related problems, self help, and local resources (feasibility of involving family or friends with medicine taking was explored). The importance of drug treatment was emphasized, side effects and their management discussed, advice about the use of reminders and cues and need to continue treatment for up to 6 months was given, and about what to do when a dose was missed.	
				0
Pyne et al, 2003	See inclusion. Depressed patients currently under treatment were not excluded.	Randomised: N=479; Completers at 12 months: N=167; Baseline characteristics: I=115, C=96; I =40.2 (14.7), C= 46.6 (14.2); I =16.5, C=14.6; Meeting on average 6.7 of the 9 DSM-criteria for major depression; 12 primary care practices located in 10 stated across the USA, with more (metropolitan) or less (nonmetropolitan) access to off-site mental health specialty care.	Training the primary care team to access, educate, and monitor depressed patients during the acute and continuation stages of depression treatment episode over 1 year. Office nurses supplement primary care physicians to provide AD medication treatment or referral to mental health counselling. The nurse in enhanced care practices reassessed each patients' symptoms, provided education about preferred treatments, asked patients to increase/maintain readiness to engage in active treatment and arranged a subsequent time to follow-up. Patients proceeded to see the physician who initiated and/or adjusted treatment as needed in this return visit. Nurses used a protocol to follow patients over the next 5-7 weeks. The continuation stage intervention was implemented on average 9 months after index visits to facilitate the reinitiation or adjustment of treatment in patients who were symptomatic at that time-point. Patient components of the continuation intervention included periodic symptom/treatment monitoring by nurse care managers who also encouraged patients to engage in active treatment. Physician components of the	SMS, DSD, CIS, DS
				12

Patients 1) reported MDD criteria (5 or more of the 9 criteria for depression in the past 2 weeks on the Inventory to Diagnose Depression), 2) were screened negative for lifetime mania, 3) were screened negative for lifetime alcohol dependence with current drinking, 4) did not meet DSM-IV criteria bereavement-related depression, 5) reported no antidepressant medication in the last month and no specialty mental health care in the last 6 months 6) had sufficient SF-36 at baseline, 6 and 12 months..

Study	Inclusion	Exclusion	Intervention	Components		
Rickles et al, 2005	Patients had no AD use in the past 4 months, were 18 years or older, were willing to pick up their antidepressant from a study pharmacist during the next 4 months, had no hearing impairment, and planned to be in the local area during the next 4 months.	Patients with a BDI-II score below 16, requiring a translator, pregnant or nursing, receiving medication for a psychotic or bipolar disorder, and/or physical conditions requiring additional caution with their depression.	N=63, Completers: N=60; I= 37.8 (10.7), C= 37.5 (13.4); I=19.4, C= 12.5; Mean BDI-II score of 28, indicating moderate depression. PGEM 28.9 (sd 8.15), CAU 27.0 (sd 8.4); 8 Wisconsin community pharmacies within a large managed care organisation.	Telephone-based education and (tele)monitoring (of antidepressant use) by community pharmacists; 3 monthly telephone calls from pharmacists providing pharmacist-guided education and monitoring (PGEM). continuation intervention included reviewing monthly patient symptom/ treatment summaries or recommendations for treatment reinitiation/adjustment.	DSD, CIS, DS	6	75
Rollman et al, 2002; Active care	Subjects with a screen positive for a mood disorder on the PQ and no obvious dementia, psychotic illness, or unstable medical condition; 2 or fewer positive responses on the CAGE alcohol screening questionnaire included on the PQ; and no language or other communication barrier that would limit the patient's ability to participate in the research assessments. In addition the protocol also required that the patient (1) have a Hamilton Depression Rating Scale score of 12 or greater, (2) report no alcohol or other substance abuse disorder within the past 2 months, (3) have no history of bipolar disorder, (4) have no active suicidal ideation, (5) be medically stable as determined from medical record review and the baseline telephone assessment, (6) have no	See inclusion.	N=211 (completing baseline assessment), N=200 (completers at 6-months); I= 44,2, C=40.8; I= 44, C=26; Current major depression; Urban academically primary care practice, the main urban primary care practice affiliated with university.	Caregivers are electronically informed of patients' diagnoses. An electronic medical record is providing feedback and evidence-based treatment recommendations for depression to PCPs via electronic medical record in a method of 1. active or 2. passive exposure or 3. usual care. If the PCP electronically expressed uncertainty about the depression diagnosis, the researcher replied with a new flag inquiring whether the patient could be scheduled to return within 4 weeks so that the PCP could again consider the diagnosis. When the PCP indicated disagreement with the depression diagnosis, another interactive e-mail message was sent after the patient's next visit. Reminders were automatically generated if the PCP did not respond to an e-mail message within 3 days. Active care PCPs who agreed with the diagnosis were exposed to 1 or more patient-specific advisory messages on the paper encounter form generated for viewing at the time of the clinical encounter. These messages were based on the AHRQ practice guideline and were modified for electronic dissemination via the EMR system. Their content varied in keeping with a PCP's earlier actions	CIS, DS	6	65

Study	Inclusion/exclusion criteria	Sample	Intervention		Follow-up	
	plans to leave the study practice within the next 6 months, and (7) not be receiving treatment at baseline for depression from a mental health professional.		as entered into the EMR system (eg, the patient was prescribed an antidepressant medication). The clinician could also view these messages online at any time. Active care PCPs were also exposed to prompts offering to schedule a follow-up appointment with their study patients whenever the interval between follow-up appointments exceeded twice that recommended by the AHRQ guideline for a given treatment phase, as determined by a researcher's review of the clinicians' encounter notes.	SMS, DSD, CIS, DS	6	80
Rost et al, 2001	Subjects meeting MDD criteria (5 or more of the 9 criteria for depression in the past 2 weeks using the Inventory to Diagnose Depression); no exclusion if currently taking antidepressant medication and/or seeing a specialty care provider.	Subjects 1) screened negative for lifetime mania, 2) with use of lithium, 3) with current alcohol dependence with current drinking, 3) with bereavement-related depression. Depressed patients currently under treatment were not excluded.	Randomised: N=479, Completers: N=432; Total: 42.6 (13.1); Total: 16.1; Meeting on average 6.7 of the 9 DSM-criteria for major depression; 12 community primary care practices across the country employing no onsite mental health professional.	Quality Enhancement by Strategic Teaming (QuEST) intervention redefining roles across the primary care team to improve the detection and management of major depression without the assistance of an onsite mental health professional; brief training to improve the detection and management of major depression. If physicians concurred with the diagnosis patients were scheduled a return visit immediately before which the nurse in enhanced care practices reassessed each patients' symptoms, provided education about preferred treatments, asked patients to do homework assignments to increase/ maintain readiness to engage in active treatment and arranged a subsequent time to follow-up. Patients proceeded to see the physician who initiated and/or adjusted treatment as needed in this return visit. Nurses used a protocol to follow patients over the next 8 weeks.		
Sherbourne et al, 2001, Unützer et al, 2001	Patients who were depressed and intended to use the clinic as a source of care for the next 12 months.	Patients younger than 18 years, with an acute medical emergency, who did not speak English or Spanish, or did not have either insurance or a public-pay arrangement that covered care delivered by the mental health specialists in the	N=835; I=44.0 (14.7), C= 42.2 (13.9); I=33.3, C=30.1; About 50% had 12-month depressive disorder (double depression, major depression or dysthymia); 46 primary care clinics in 6 USA managed primary care	QI programmes, encouraging initiation and adherence to appropriate treatments for depression, included training local experts and nurse specialists to provide clinician and patient education, assessment, and treatment planning, plus either nurse care managers for medication follow-up (QI-meds) or access to	SMS, DSD, CIS, DS	24	85

	interventions (this criterion excluded all fee-for-service patients in 1 site and half of them in another). In the pilot month for the first site, patients screening positive for bipolar disorder or alcoholism were excluded, but not for the main study.	organisations (1 with 2 seperate regions), diverse in geography and organisation and to oversample Mexican Americans. The organisations included staff and network model multispecialty group practices and rural managed public health clinics. Patients had prepaid or managed fee-for-service (including Medicare and Medicaid) coverage. Uninsured patients were included in 1 site. All 7 had a carve-out mental health plan, 4 had in-house mental health providers, 2 had multiple provider groups, the percentage of patients capitated ranged from 50% to 100%.	trained psychotherapists (QI-therapy). QI programs involved institutional commitment to QI, training local experts and nurse specialists to provide clinician and patient education, identification of a pool of potentially depressed patients, and either nurses for medication follow-up or access to trained psychotherapists. The nurses were asked to contact intervention patients for an initial visit (assessment, education, and activation) 2 weeks after the screening visit. The primary care clinician was asked to consider this information in formulating a treatment plan with the patient. In the QI-meds intervention, the nurse specialists were trained to provide follow-up assessments and support adherence through monthly contacts for 6 or 12 months (randomized at the patient level). Patients in the QI-meds intervention had access to usual practice therapists, but not the study cognitive behavioural therapy (CBT).In the QI-therapy intervention, the study trained local psychotherapists to provide manualised individual and group CBT for 12 to 16 sessions. Patients could access other therapy for the usual co-payment. Brief (4-session) CBT was suggested as an option for patients with minor depression.			
Simon et al, 2000; Feedbac k only	All patients at participating clinics who had received new prescriptions for antidepressants, with "new" defined as no antidepressant use in the previous 120 days.	Patients who had not been diagnosed with depression at any visit (non-depression indication for prescription); had been diagnosed with bipolar disorder or psychotic disorder in the previous 2 years; had been diagnosed with alcohol or other substance misuse in the previous 90 days; or had visited a psychiatrist in the previous 90 days.	N=417; I=46.5 (14,3), C=46,8 (15,3); I=30, C=28; Current depression; Feedback only 1.67 (0.72), CAU 1,74 (,77); 5 primary care clinics of Group Health Cooperative of Puget Sound, an organisation serving around 450 000 members in Washington state. A typical primary care clinic has around 20 000 members with a	Feedback only comprised feedback and algorithm based recommendations to doctors on the basis of data from computerised records of pharmacy and visits.	CIS, DS	6	65

staff of eight to 10 doctors, 3-5 registered nurses, and 8-10 licensed practical nurses or medical assistants. On average, adult members make four to five visits annually. Separate mental health clinics provide a range of services with emphasis on brief psychotherapy, pharmacotherapy, and group therapy. No referral or authorisation is required for uptake of mental health care.

Simon et al, 2004; TCM	Adult patients starting a new episode of antidepressant medication for treatment of depression (ie, filled antidepressant prescription, diagnosis of depression, and no antidepressant use in the prior 90 days).	Patients 1) already in remission when contacted (SCL<.05), 2) already receiving psychotherapy (ie, any specialty mental health visit in the last 90 days), 3) with a diagnosis of bipolar disorder or schizophrenia in the last 2 years, 4) with a cognitive, language, or hearing impairment severe enough to preclude participation.	N=402; I= 44.9 (15.3), C=44.0 (16.0); I=28, C=22; SCL score CAU: 1.55 (0.62), TCM: 1.54 (0.61), PHQ score CAU: 15.0 (5.5), TCM: 15.1 (5.5), on average, participants reported a moderate level of depressive symptoms at baseline (2-4 weeks after starting treatment); 7 group-model primary care clinics of Group Health Cooperative, a prepaid health plan serving approximately 500000 Washington State residents enrolled via employer and individual contracts and via risksharing contracts with Medicare and Medicaid programmes. Membership is demographically similar to the Seattle area population.	A telephone care management (TCM) programme including at least 3 outreach calls, feedback to the treating physician, and care coordination; usual care plus care management integrated with a structured 8-session cognitive-behavioural psychotherapy programme delivered by telephone. Each session began with a brief structured assessment of depressive symptoms, medication use, and adverse effects.	SMS, DSD, CIS, DS	6	75
Simon et al, 2004; TCM+	See Simon et al, 2004; TCM.	See Simon et al, 2004; TCM.	N=393; I=44.7 (15.7), C=44.0 (16.0); I=26, C=22; SCL score CAU: 1.55 (0.62), TCM+: ...	A telephone care management (TCM) programme (including at least 3 outreach calls, feedback to the treating physician, and care	SMS, DSD, CIS, DS	6	75

Study	Population / Inclusion	Exclusion / Notes	Baseline	Intervention	Sample			
			1.52 (0.58), PHQ score CAU: 15.0 (5.5), TCM+: 14.6 (5.1), on average, participants reported a moderate level of depressive symptoms at baseline (2-4 weeks after starting treatment); 7 group-model primary care clinics of Group Health Cooperative, a prepaid health plan serving approximately 500000 Washington State residents enrolled via employer and individual contracts and via risksharing contracts with Medicare and Medicaid programmes. Membership is demographically similar to the Seattle area population.	coordination) integrated with a structured 8-session cognitive-behavioural psychotherapy programme delivered by telephone. The telephone psychotherapy intervention included all aspects of the telephone care management programme plus a structured 8-session cognitive behavioural psychotherapy programme adapted from an earlier pilot study (Tutty et al. 2000). Intervals between sessions 2-4 were weekly and between later contacts ranged from 1 to 4 weeks depending on need and patient preference. As with the telephone care management programme, each session began with a brief structured assessment of depressive symptoms, medication use, and adverse effects. The telephone psychotherapy programme was an addition to, rather than a substitute for, telephone care management. Therapy sessions were designed for completion in 30 to 40 minutes. Sessions focused on increasing pleasant and rewarding activities, identifying, challenging, and distancing from negative thoughts, creation of a personal self-care plan covering medication use, self-monitoring, and self-management skills.		SMS, DSD, DS	3	65
Solberg et al, 2001	Patients with a primary care clinician visit; an International Classification of Diseases, 9th revision, code for depression at that visit; and no code for schizophrenia, dementia, or chemical dependence in the past year.	Pre-intevention participants were excluded from the post-intervention sample.		Continuous Quality Improvement intervention. A multidisciplinary team from the three intervention clinics developed and implemented a graded set of five care management options, ranging from watchful waiting (nurse telephone call in 4 to 6 weeks) to mental health management, which clinicians could order for their patients with depression. Care management options included self management support, care guidance, collaborative care and mental health management.	N=433 before intervention, Completers: N=359; NR, 18-40 y I=29%, C=27%; 41-60y I=42%, C=39%; >60y I=29%, C=4%; I= 28, C=30; Depressed (score ≥6 on CES-D) 79% (in both conditions); 9 primary care clinics in greater Minneapolis-St. Paul, Minnesota: 3 volunteer CQI clinics and 6 control.			
Swindle	Patients with a diagnosis	Patients with		Integrating generalist and specialist	Randomised: N=268,	SMS, DSD, CIS	12	85

et al, 2003	of major depression, dysthymia, or partially remitted major depression using PRIME-MD structured clinical interview, at least 2 GMC visits during the past year and plans to receive ongoing primary care from the GMC, access to telephone.	incompetence for interview (active psychosis, dementia documented in medical chart), residents of a nursing home, actively suicidal, seen in a VAMC mental health program (made a visit during the previous 30 days and had a future appointment scheduled), active cocaine or opiate abuse, history of bipolar disorder, terminally illness.	Completers at 3 months: N=246, Completers at 12 months: N=222; I=56.4 (11.7); C=56.2 (13.1); I =97, C=96; PRIME-MD diagnosis MDD: I=31%, C=27%. MDD and dysthymia: I=63%, C=55%, dysthymia only: I=9%, C=10%. Partially remitted MDD: I=1%, C=4%, BDI mean: I=20.7 (sd 9.1), C 21.9 (sd 7.9), Pre-existing diagnosis of depression: I=18%, C=11%; 2 Veteran Affairs Medical Center general medicine clinic (GMC) firms of the Roudebush VAMC, a university-affiliated VAMC staffed by board-certified internists and internal medicine house officers providing continuous primary care to over 10,000 veterans.	care (integrated primary care intervention): a mental health clinical nurse specialist designed a treatment plan, implements that plan with the primary care physician, and monitors patients via telephone or visits at 2 weeks, 1 month and 2 months. CNSs designed based on PRIME-MD interview and medical record an initial treatment plan and recommended an initial 8-week course of antidepressant (SSRIs generally as recommended as first choice), for patients already on AD and still symptomatic the CNs would consider changing medication agent or dosage, for patients unable to take AD or failing an adequate trial of several ADs an appointment to the mental health clinic was scheduled. The CNS would communicate the initial treatment plan to the PCP and discuss it together with the patient and implement it. Monitoring through telephone and/or in-person contacts was to occur at 2 weeks (CNSs were to evaluate symptoms, review side effects and encourage compliance with AD) and 2 months following initial visit (CNSs were to contact patients to insure that AD were properly tirated and review symptom remission). For patients not improved, non-compliant, or with medication problems a return visit for further evaluation and modification in treatment was encouraged. If referrals were made the CNS would serve as the liaison between psychiatry and GMC providers.	
Trivedi et al, 2004	Male and female outpatients 18 years or older with a clinical diagnosis of MDD (psychotic or nonpsychotic). Patients entered ALGO if their treating physician judged that they required an antidepressant medication change or were starting	Patients were excluded if they had schizophrenic, bipolar, or schizoaffective disorder or a primary diagnosis of an obsessive-compulsive or eating disorder (anorexia nervosa or bulimia nervosa), requiring inpatient hospitalization for detoxification at the time of study entry, receiving	N=547 evaluable patients, Analytic sample: N=350 (postmatched based on symtoms and length of illness); I=41.1 (11.4), C=41.8 (10.5); I=20.0; C=20.0; Major depressive disorder mean length of illness: I=13.0 y (12.4); C=14.3 y (11.4), Psychotic	ALGO included 2 consensus-driven, medication management algorithms (one each for psychotic and non-psychotic forms of MDD) and expert consultation (offered on biweekly teleconference); and on-site clinical support from clinical coordinators and a patient and family education programme provided by the clinical coordinators. This intervention package was intended to optimize pharmacotherapy, thereby	SMS, CIS, DS 12 65

| | | | | SMS, DSD, CIS, DS | 12 | 85 |

enhancing clinical outcomes. Each physician implemented ALGO in close collaboration with a clinical coordinator. A 7-step medication algorithm for non-psychotic MDD and a 5-step algorithm for psychotic MDD were provided. Most steps in each algorithm included multiple treatment options, with earlier steps including those treatment options with the most evidence and the best risk-benefit ratios. Multiple tools were used to enhance adherence to the algorithm. A detailed treatment manual was used for initial didactic training and ongoing consultations with clinicians with critical decision points (eg, weeks 4, 6, 8, 10, and 12) for each medication when revisions in treatment strategies or tactics were to be undertaken based on degree of symptom change and side effect burden. Symptom severity and side effect burden were routinely monitored at each treatment visit to guide treatment implementation, with the aim of ensuring an adequate duration and dose of medication. Clinical assessments at each visit included a global assessment of symptoms and associated symptoms, IDS-C30 and IDS-SR30, and side effect burden by a 10-point global scale. A standard clinical record form was completed at each clinic visit by those implementing the ALGO intervention. The symptom severity assessments were conducted by clinical coordinators before the physician visits. Each ALGO patient also received a stepwise education package that provided information about the disease, prognosis, treatment options, and medication side effects. This package encouraged patients to participate in treatment decisions and adhere to the treatment.

The Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) collaborative care management programme for late-life

mental retardation services, or participating in an Assertive Community Treatment programme.

symptoms: I=17.7, C=18.3; 4 ALGO clinics, 6 TAU clinics, and 4 clinics that offer TAU to patients with MDD but provided ALGO for schizophrenia or bipolar disorder.

antidepressant therapy. In TAU, patients were also recruited if their quarterly, routinely administered 24-item Brief Psychiatric Rating Scale (BPRS-24) total score was higher than the median for that clinic's routine quarterly evaluation of each patient. Once approached, another BPRS-24 interview was conducted. Patients with BPRS-24 total scores no more than 1 SD below enrolled ALGO patient average scores were asked to participate.

Patients with current drinking problems (a score of 2 on the CAGE questionnaire); a history of

N=1801; I=71 (7.4); C=71.4 (7.6); I=36, C=34; Major depression: 17%,

Patients aged 60 years or older, with plans to use one of the participating clinics as

Unützer et al, 2002

	the main source of general medical care in the coming year, and a diagnosis of current major depression or dysthymic disorder according to the SCID.	bipolar disorder or psychosis, in ongoing treatment with a psychiatrist, meeting screening criteria for severe cognitive impairment defined by a score of less than 3 on a 6-item cognitive screen, at acute risk for suicide and needing immediate care.	dysthymic disorder: 30%, both: 53%, 2 or more prior episodes: 71%, mean SCL-20 depression score: 1.7 (moderate to severe depression), suicide thoughts in 6% in past month; 18 primary care clinics from 8 health care organisations in 5 states (including Veterans Affairs, Private Group Practices, HMO, etc).	depression includes key components of evidence-based models for chronic illness care: collaboration among primary care practitioners, patients, and specialists on a common definition of the problem, development of a therapeutic alliance, a personalised treatment plan that includes patient preferences, proactive follow-up and outcomes monitoring by a depression care manager, targeted use of specialty consultation, and protocols for stepped care. Intervention patients had access for up to 12 months to a depression care manager who was supervised by a psychiatrist and a primary care expert and who offered education, care management, and support of antidepressant management by the patient's primary care physician or a brief psychotherapy for depression, Problem Solving Treatment in Primary Care.		65
Worrall et al, 1999	Not specified.	Not specified.	N=147 patients, N=42 physicians; I=43.2, C=45.7, SDs NR; I=34.1, C=23.2; DSM-IV diagnoses of depression: I=93.4, C=94.6; 42 fee-for-service physicians, recruited after a 3-month pilot.	Educational intervention based on clinical practice guidelines (CPG) formulated by the Canadian Medical Association for managing depression. A 3h workshop by a psychiatrist and family physician on clinical practice guidelines for depression with information on the epidemiology of depression, an explanation of the CPGs and a discussion of prepared cases. Physicians were also invited to discuss their own cases with reference to specific difficulties they had in diagnosing and treating depression. In addition access to a psychiatrist for follow-up consultation was readily available for advice on patient management at a specific time each week.	DSD, DS	6

Type of care	Unit	Unit cost price in 2007 Euro
General Practitioner	Consult	21.50
Psychologist/Psychotherapist	Session	69.88
Psychiatrist	Session	86.01
Social Worker	Contact	37.63
Antidepressants	Prescription	34.99
General Practice Nurse	Contact	39.64
Telephone consult	Call	34.43
Self-help book	Book	37.63
Information leaflet	Leaflet	5.38
Social Psychiatric Nurse	Contact	43.01
Group therapy	Hour	10.75
Crisis intervention	Day	150.52
Inpatient care	Day	258.03
Day care	Day	96.76
Homecare	Hour	10.75
Psychiatric home care	Hour	43.01
Other out-patient care	Hour	32.25

Table 8S2 Estimates of care consumption in guideline-congruent care and care as usual (CAU) for mild episodes of major depressive disorder: type of care, number of units and costs of care per patient (in euros) - Appendices

Type of care	Coverage, units	Costs	Coverage, units	Costs	Coverage, units	Costs	Coverage, units	Costs	Coverage, units	Costs	Coverage, units	Costs
	Guideline congruent care: Step 1 and 2											
	Step 1-main		Step 1-lower		Step 1-higher		Step 2 -main		Step 2-lower		Step 2-higher	
General Practitioner	3	64.5	2	43	6	129	3	64.51	2	43	6	129
General Practice Nurse	1*30'	19.82	1*30'	19.82	1*30'	19.82						
Telephone consult	2*20'	22.95	0	0	5*20'	57.38						
Selfhelp book	1	37.63	1	37.63	1	37.63						
Information leaflet							1	5.38	1	5.38	1	5.38
Psychologist/ Psychotherapist							5*45'	262.05	2*45'	104.82	6*45'	314.46
Medication prescription												
Psychiatrist												
Social worker												
Social Psychiatric Nurse												
Group therapy												
Total costs in 3 months		**144.9**		**100.45**		**234.38**		**331.49**		**153.2**		**448.84**
Total in 6 months								**476.84**		**253.65**		**692.67**

Type of care	Coverage, units	Costs	Coverage, units	Costs	Coverage, units	Costs	Coverage, units	Costs
	CAU							
	CUA scenario-main		CAU scenario-low		CAU scenario-high		Scenario 2c	
General Practitioner	3+50%*3	96.75	50%*3	32.25	6	129	50%*3	32.25
General Practice Nurse								0
Telephone consult								0
Selfhelp book								0
Information leaflet			0					0
Psychologist/ Psychotherapist	1*45'	52.41	1*45'	5241	6*45'	314,46	44%*6.5	199.86
Medication prescription	42%*3'	44,.9	42%*1,6	23.51	70%*3	73,48	80%*11	307.91
Psychiatrist	1*3'	4,3	1*3'	4,3	1*3'	4,3	40%*1.5	51.61
Social worker	1*5'	3,14	1*5''	3,14	1*5'	3,14	25%*4	37.63
Social Psychiatric Nurse							40%*6	103.22
Group therapy							64%*17	116.96
Total costs in 3 months		**200.69**		**115.61**		**524,38**		
Total in 6 months		**401.38**		**231.22**		**1048,76**		

Type of care	Coverage, units	Costs	Coverage, units	Costs	Coverage, units	Costs
	Guideline-congruent care					
	Scenario-main		GCC-lower		GCC-higher	
General Practitioner	16	344	8	172	32	688
Psychologist/ Psychotherapist	25%*16*60'	79.52	25%*16*60	279.52	50%*16*60'	559.04
Medication prescription	4	139.96	3	104.97	4	139.96
Information leaflet	1	5.38	1	5.38	1	5.38
Psychiatrist	25*16*60'	344.04	25*16*60'	344.04	25*16*60'	344.04
Social Psychiatric Nurse						
Social worker						
Group therapy						
Crisis intervention						
Inpatient care						
Daycare						
Homecare						
Psychiatric homecare						
Other outpatient care						
Total costs in 8 months		**1112.9**		**905.91**		**1736.42**

Type of care	Coverage, units	Costs	Coverage, units	Costs	Coverage, units	Costs
	CAU					
	CAU-main		CAU-lower		CAU-higher	
General Practitioner	50%*3	32.25	50%*3	32.25	50%*3	32.25
Psychologist/ Psychotherapist	44%*6,5	199.86			44%*6,5	199.86
Medication prescription	80%*11	307.91	80%*5	139.96	80%*11	307.91
Information leaflet						
Psychiatrist	40%*1,5	51.61	40%*1,5	51.61	40%*1,5	51.61
Social Psychiatric Nurse	40%*6	103.22	40%*6	103.22	40%*6	103.22
Social worker	25%*4	37.63	25%*4	37.63	25%*4	37.63
Group therapy	64%*17	116.96	64%*17	116.96	64%*17	116.96
Crisis intervention					3%*1*12/18	3.01
Inpatient care					8%*51	1052.76
Daycare					7%*9	60.96
Homecare					7%*3	2.26
Psychiatric homecare					2%*35	30.11
Other outpatient care					8%*8	20.64
Total costs in 8 months		**849.50**		**481.63**		**2019.18**

Group	Parameter	Distribution	Source
Guideline-congruent care for mild MDD	Healthcare costs month 1-3	Triangular (peak: 144.9, min: 100.45, max: 243.83)	Spijker et al, 2002; Boer et al 2004; Spijker et al, 2013
Guideline-congruent care for mild MDD	Healthcare costs month 4-6	Triangular (peak: 331.94, min: 153.2, max: 448.84)	Spijker et al, 2002; Cuijpers et al, 2007b; Spijker et al, 201386.01
Guideline-congruent care for moderate-severe MDD	Healthcare costs month 1-8	Triangular (peak: 1112.9, min: 905.91, max: 1736.42)	Spijker et al, 2002; Spijker et al, 2013
CAU for mild MDD	Healthcare costs month 1-6	Triangular (peak: 401.38, min: 231.22, max: 1048.76)	Spijker et al, 2002; van Roij-en et al, 2006; Bosmans et al, 2008; Nuijen et al, 2008; Braspenning et al, 2004; SFK, 2007; CVZ, 2008; Gardarsdottir et al, 2007
CAU for moderate-severe MDD	Healthcare costs month 1-8	Triangular (peak: 849.5, min: 481.63, max: 2019.18)	Spijker et al, 2002; Stant et al, 2008; Bosmans et al, 2008; Nuijen et al, 2008; Braspenning et al, 2004; SFK, 2007; CVZ, 2008; Gardarsdottir et al, 2007
Guideline-congruent care + CAU for mild MDD	Baseline QOL	Fixed: 0.81	Kruijshaar et al, 2005
Guideline-congruent care + CAU for mode-rate-severe MDD	Baseline QOL	Fixed: 0.49	Kruijshaar et al, 2005
Guideline-congruent care for mild MDD	Effect size MI	Gaussian (mean: 0.84, SD = (1.02 - 0.84) /1.96)	Boer et al 2004
Guideline-congruent care for mild MDD	Effect size PST	Gaussian (mean: 0.83, SD = (1.21 - 0.83) /1.96)	Cuijpers et al, 2007b
Guideline-congruent care for moderate-severe MDD	Effect size PT	Gaussian (mean: 0.531, SD = (0.717 - 0.531) /1.96)	Haby et al, 2006; Maat et al, 2007
All	Conversion Cohen d effect size to QOL gains	Uniform (min: 0.139, max: 0.172)	Sanderson et al, 2004
All	Recovery curve	Lognormal (meanlog: 3.09, SDlog: 1.24) with VCOV matrix for additional parameter un-certainty	Vos et al, 2004; Werf et al, 2006; Berg et al, 2011; Smit et al, 2006; Cuijpers et al, 2007a
All	Relapse curve	Lognormal (meanlog: 2.34, SDlog: 3.87)	Vos et al, 2004; Werf et al, 2006; Berg et al, 2011; Smit et al, 2006; Cuijpers et al, 2007a

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Brief summary

The case for stepped care

Exploring the applicability and cost-utility of stepped-care strategies in the management of depression

The nature of depressive disorder, with substantial impact on quality of life for patients and their relatives, the high prevalence, substantial disease burden, and high accompanying costs, are making depressive disorder an obvious case example for stepped care in this thesis, especially considering the availability of clinical practice guidelines.

Stepped care, in this thesis, is concurrently about achieving better treatment outcomes for individual patients through supporting clinical decision making (a microperspective); integrating service delivery (a mesoperspective); and improving the cost-utility of care (a macroperspective). The stepped-care depression model described in chapter 2, represents an alignment of these three perspectives in such a way that improvement from any one of these, adds value as viewed from all perspectives. Stepped care offers the possibility of improvements on the micro-, meso- and macrolevel simultaneously. The depression care management process model presented in chapter 3 is developed to provide a framework for improvement strategies on the micro-, meso- or macrolevel of care.

We explore the applicability and cost-utility of stepped-care strategies in the management of depression, and investigate if and how stepped-care treatment strategies and stepped-care service delivery can add value to depression care. The studies conducted for this thesis generate evidence that stepped-care treatment strategies can be feasible, acceptable, effective, and potentially cost-effective. The empirical studies (in chapters 4 to 6) contribute to advancing patient-centred care in daily practice as follows: by structuring treatment options across the care continuum, with evaluation criteria for stepping up and sequencing interventions, by supplying practical tools that enable care professionals to choose evidence-based treatment strategies and adjust these to the patient's needs, and by demonstrating the feasibility and acceptability of implementing stepped care in routine practice. The meta-analysis performed for this thesis (in chapter 7) highlights that taking account of depression severity and other sources of heterogeneity is effective and contributes to person-centered care. The health-economic depression state-transition modelling study (in chapter 8) shows that stepped-care algorithms can be cost-effective. These algorithms enable care professionals to stratify for the

nature, duration, severity and recurrency of depression. The algorithms for mild episodes of depression aim to reduce over-treatment and the inappropriate use of antidepressants, while the algorithms for moderate and severe depression aim to offer adequate treatment rapidly, reducing under-treatment.

The main conclusions for healthcare policy and practice to be drawn from this thesis are, first, in the treatment of depression, stepped-care strategies are essential in obtaining optimal treatment outcomes for patients and, second, when improving or controlling depression care from a meso- or macroperspective, it is tremendously important to remain a patient-centred view on depression care. Healthcare policy can improve depression care by shaping the conditions to perform stepped-care strategies. Care professionals can improve patient outcomes by applying stepped-care tools for clinical decision making, when uncertainty about the individual prognosis prevails.

Stepped care enables stratifying care to the patient's profile and a person-centred approach in daily practice. As long as this adds value to depression care, it holds that every patient with a depression is *the case for stepped care.*

De casus voor stepped care

Exploratie van de toepasbaarheid en kostenutiliteit van stepped-care strategieën bij depressiemanagement

De meerwaarde van stepped care

Depressieve stoornissen zijn veelvoorkomend. Het doormaken van een depressie en de gevolgen ervan zijn ingrijpend. De kwaliteit van leven kan aanzienlijk verminderen, ook voor de naastbetrokkenen. Depressie kent verschillende verschijningsvormen. Welke behandeling het meeste baat biedt, kan van persoon tot persoon variëren. Het nemen van beslissingen over het beste behandelbeleid is altijd, bij iedere patiënt, omgeven door onzekerheid, zoals onzekerheid over de diagnose, de prognose, de behandelrisico's en te verwachten behandeleffecten. Met deze onzekerheid dienen zorgprofessionals rekening te houden, waarbij de risico's van zowel overbehandeling als onderbehandeling moeten worden afgewend. Stepped care (getrapte zorg) biedt een meerwaarde in de zorg voor depressie, zoals wordt onderbouwd in dit proefschrift. Stepped care levert namelijk passende zorg op; zo licht als mogelijk en zo intensief als nodig is. De definitie van stepped care luidt: "Stepped care is zorg die zo licht als mogelijk en tegelijkertijd zo intensief als nodig is, rekening houdend met de aard, duur, ernst en het beloop van symptomen - of fasen van depressie - in het nemen van beslissingen over een passend individueel behandelplan om behandeldoelen te bereiken door, ten eerste, interventies die lichter in intensiteit zijn te prefereren boven intensievere interventies indien dit passend en aannemelijk is, en, ten tweede, door het behandelplan aan te passen en over te stappen op vervolginterventies, naargelang het monitoren van de behandelresponse aangeeft dat dit nodig is."

Er zijn diverse wetenschappelijk onderbouwde behandelvormen beschikbaar, zoals beschreven in de Multidisciplinaire richtlijn Depressie (Spijker et al. 2013) en in de Zorgstandaard Depressieve stoornissen (Meeuwissen, van Bon et al. 2018). De multidisciplinaire richtlijn geeft aanwijzingen voor gedeelde besluitvorming, het - met de patiënt gezamenlijk - evalueren van behandeluitkomsten en, indien nodig, tijdig overstappen op beter passende interventies, volgens stepped-care behandel-strategieën. Hierbij wordt rekening gehouden met persoonlijke voorkeuren en omstandigheden. In alle uitgevoerde studies in dit proefschrift, zijn de interventies en de stappenvolgorde, voor het overwegen ervan, geheel gebaseerd op aanbevelingen volgens de multidisciplinaire richtlijn en conform de zorgstandaard voor depressie.

Een micro-, meso- en macroperspectief

Stepped care kan bijdragen aan het verbeteren van de depressiezorg vanuit drie perspectieven:

1 Een microperspectief: door het verbeteren van de behandeluitkomsten voor patiënten en het ondersteunen van hulpverleners bij de klinische besluitvorming over het behandelbeleid aan de hand van stepped-care behandelstrategieën.

2 Een mesoperspectief: door het verbeteren van de kwaliteit van de organisatie van de depressiezorg, zodat deze de voorwaarden biedt voor stepped-care behandelstrategieën.

3 Een macroperspectief: door het verbeteren van de kostenutiliteit van de depressiezorg met het toepassen van stepped-care behandelalgoritmes.

Volgens het stepped-care model in dit proefschrift geeft verbetering van de zorg vanuit één van deze drie perspectieven, ook verbetering in de beide andere perspectieven. Op basis van de uitgangspunten van het stepped-care model kunnen stepped-care programma's, verbeterstrategieën, behandelstrategieën, behandelalgoritmes en andere kwaliteit verbeterende of beslissingsondersteunende instrumenten en heuristieken worden ontwikkeld. Deze maken de te overwegen behandelopties en de klinische beslissingen die zorgprofessionals en hun patiënten gezamenlijk moeten nemen, expliciet.

Stepped care is geen nieuw concept in de geestelijke gezondheidszorg, maar de wijze van toepassen ervan varieert en de kosteneffectiviteit is nog onvoldoende onderzocht.

1 Algemene inleiding

Hoofdstuk 1, de algemene inleiding, introduceert de kernbegrippen in dit proefschrift, beschrijft relevante ontwikkelingen in relatie tot stepped care en bespreekt de toepasbaarheid ervan in de depressiezorg. Ook worden de onderzoeksvragen en doelstellingen van dit proefschrift beschreven, wordt uiteengezet wat de zorg voor depressieve stoornissen tot een geschikte casus maakt voor dit proefschrift en wordt de wijze waarop de onderzoeksvragen worden geadresseerd besproken. Het proefschrift is vervolgens opgebouwd uit drie delen.

I Stepped care en depressiemanagement

Deel I, waarin de uitgangspunten van het stepped-care model (getrapte-zorgmodel) en van het Chronic Care Model (chronische-zorgmodel) vanuit het micro-, meso- en macroperspectief uiteen worden gezet, legt de basis voor het verdere proefschrift.

2 Stepped care: concept en doelen

Dit hoofdstuk gaat in op de meerwaarde van stepped care in de depressiezorg. Stepped care is, zoals wordt beschreven, in de eerste plaats een geschikte behandelstrategie voor klinische besluitvorming bij onzekerheid over de juiste behandeling voor de patiënt. Stepped-care strategieën kunnen zorgprofessionals ondersteunen, telkens wanneer een beslissing genomen moet worden over wat nu de beste behandeling is voor de patiënt. Dit is het geval als evidentie over mogelijke matchingsfactoren tussen de patiënt en een specifieke behandeling, waarbij een differentieel effect van de behandeling bij deze patiënt verwacht kan worden, niet voorafgaand bekend kan zijn. Essentieel hierbij is dat stepped-care strategieën rekening houden met individuele patiëntkenmerken en met persoonlijke voorkeuren en omstandigheden van de patiënt.

De kernelementen van stepped-care strategieën betreffen het intensiveren van de zorg naargelang de behoeften van de patiënt, door: 1. Kiezen van de minst intensieve interventie waarmee de behandeldoelen bereikt kunnen worden, rekening houdend met de aard, duur, ernst en het beloop van de depressiesymptomen; 2. Regelmatig monitoren van de ernst en het beloop van de depressiesymptomen en periodiek evalueren van de behandeling en de behandeluitkomsten; 3. Aanpassen van het individuele behandelbeleid door tijdig overstappen op een intensievere interventie, totdat de behandeldoelen zijn bereikt. Als de behandeldoelen zijn bereikt, bijvoorbeeld als de symptomen in remissie zijn, wordt deze strategie herhaald voor nieuwe behandeldoelen, zoals terugvalpreventie of persoonlijk herstel.

3 Depressiezorg-management: concept en doelen

Dit hoofdstuk gaat in op hoe stepped care de vier componenten van het chronische-zorg model kan versterken:

i *Ondersteuning van zelfmanagement.* Het ondersteunen van zelfmanagement wordt vaak ingezet als een eerste-stap interventie in stepped-care modellen. Gedurende vervolgstappen in de behandeling kan het ondersteunen van het zelfmanagement van de patiënt helpen om persoonlijk herstel te bereiken.

ii *De organisatie van het zorgsysteem.* Stepped care voorziet in een sturingsprincipe voor het inrichten van de zorgverlening en het alloceren van zorg. Door evidence-based interventies te structureren in een stappenvolgorde met toenemende intensiteit, voor het gehele zorgcontinuüm, wordt het coördineren van integrale zorgprocessen vereenvoudigd. Het monitoren van de voortgang en het overstappen op een volgende interventie vindt plaats op basis van expliciete criteria. Stepped care is zo, met andere woorden, een manier om de zorgverlening te organiseren. Geïntegreerde zorgverlening, met hoge kwaliteit van zorg en efficiënte zorgprocessen, verbetert de condities voor zorgprofessionals om individuele stepped-care strategieën uit te voeren en kan, bovendien, onzekerheid rondom het nemen van beslissingen over het behandelbeleid verminderen.

iii *Beslissingsondersteuning.* Evidence-based richtlijnen en andere kwaliteitszorgstandaarden of beslissingsondersteunende tools die hiervan kunnen worden afgeleid, ondersteunen de klinische besluitvorming en dragen zo bij aan het bereiken van betere behandeluitkomsten voor patiënten, zoals in stepped-care behandelstrategieën. Ook ondersteunt het inrichten van zorgprocessen op basis van kwaliteitsstandaarden de klinische besluitvorming, zoals in stepped-care zorgverlening.

iv *Klinische informatiesystemen.* Klinische informatiesystemen voorzien in tijdige en relevante data op zowel patiëntniveau als op geaggregeerd niveau om effectieve en efficiënte zorg te faciliteren. Het monitoren en evalueren van zorgprocessen is fundamenteel in depressiezorg-management. De focus op het monitoren en evalueren van zorgprocessen binnen zorgorganisaties ligt bij stepped care op het optimaliseren van individuele behandelstrategieën en gezondheidswinst voor patiënten.

In dit hoofdstuk wordt bovendien een procesmodel voor kwaliteitsverbetering van de depressiezorg geïntroduceerd. Dit model biedt een kader voor het implementeren en evalueren van verbeterstrategieën op het gebied van kwaliteit en efficiëntie van de zorg. Het gebruik en de inbedding van kwaliteitsstandaarden in de praktijk kan volgens dit model worden bevorderd met verbeterstrategieën vanuit mesoperspectief, om de kwaliteit en efficiëntie van de zorgverlening te verbeteren. Feedbackloops tussen het patiëntniveau (microperspectief) en het zorgprocesniveau van de zorg-verlening (mesoperspectief), maken het mogelijk te sturen op informatie die

relevant is voor het kunnen bijstellen van de individuele behandelstrategie. Op deze wijze kunnen de behandeluitkomsten voor patiënten worden verbeterd. Tegelijkertijd kan een verbetercyclus op basis van deze sturingsinformatie de kwaliteit en efficiëntie van zorgprocessen verbeteren. De patiëntgerichte focus is cruciaal om value-based zorg te bereiken.

II Implementeren van stepped care

Deel II van het proefschrift gaat over de implementatie van stepped care, *in casu* depressie. Drie empirische studies illustreren hoe de implementatie van stepped-care strategieën kan worden uitgevoerd. Deze implementatiestudies zijn, voor zover bekend, de eerste studies in Nederland op dit gebied. De strategieën voor het verbeteren van de kwaliteit en efficiëntie van de zorgverlening (het mesoniveau in het stepped-care model) resulteerden in verbeterde patiëntenuitkomsten (het microniveau in het stepped-care model). Deze empirische studies dragen als volgt bij aan het verbeteren van de praktijk van de depressiezorg:

1 Door evidence-based behandelopties te structureren in opeenvolgende behandel-opties, in het gehele zorgcontinuüm, op basis van de multidisciplinaire richtlijn, met bijbehorende evaluatiecriteria voor het overwegen of overstappen op een volgende interventie.

2 Door praktische beslistools aan te reiken die zorgprofessionals ondersteunen bij het kiezen uit verschillende behandelopties en bij het aanpassen van evidence-based behandelstrategieën aan persoonlijke behoeften van patiënten.

3 Door de toepasbaarheid en de aannemelijkheid ervan te demonstreren wanneer stepped care wordt geïmplementeerd in de dagelijkse zorgpraktijk.

De uitkomsten van deze studies zijn in lijn met de bevindingen van door andere onderzoekers uitgevoerde gecontroleerde studies.

4 De uitvoerbaarheid van een stepped-care programma voor depressie-management

De studie in hoofdstuk 4 betreft de implementatie van een stepped-care programma voor depressiemanagement in een tweeënhalf jaar durende pilot-studie. Onderdeel van dit programma is een stepped-care algoritme voor de diagnostiek en behandeling van depressie, gebaseerd op de Multidisciplinaire richtlijn voor Depressie. Zorgprofessionals die werkten met het algoritme werden ondersteund door een liaison-consultatie functie vanuit de gespecialiseerde ggz, waarbij de huisarts consult kon vragen aan een psychiater of psychotherapeut in de instelling voor geestelijke gezondheidszorg.

Adherentie door huisartsen en consultatie-gevende zorgprofessionals aan het stepped-care programma bleek 96% te zijn in deze pre-post studie, gemeten met interviews met 28 zorgprofessionals over 235 patiënten met lichte, matige of ernstige depressie. Het percentage verwezen patiënten naar de gespecialiseerde ggz nam significant af (van 26% naar 21%; p=.0180), waardoor meer patiënten hun behandeling konden vervolgen in de huisartsenzorg of basis-ggz. Consultatie-verzoeken kwamen meer in overeenstemming met het stepped-care programma. We concluderen dat het implementeren van een stepped-care programma voor depressie haalbaar en uitvoerbaar is in een multidisciplinaire zorg-setting en geassocieerd is met minder verwijzingen naar de gespecialiseerde ggz.

5 Aannemelijkheid van stepped care en kwaliteitsverbetering van de depressiezorg

De studie in hoofdstuk 5 betreft kwaliteitsverbetering van de depressiezorg op mesoniveau vanuit een stepped-care benadering, met als doel het laten samenwerken van zorgprofessionals en het inzetten van praktische tools om de Multidisciplinaire richtlijn Depressie toe te passen. Een vereenvoudigd stepped-care model voor depressie, bestaande uit een eerste-stap behandeling voor niet-ernstige depressie (kortdurende of milde symptomen) met niet-intensieve behandelingen, en een tweede-stap behandeling voor patiënten met een ernstige depressie en voor patiënten die niet voldoende opknapten na 6-12 weken met een eerste-stap behandeling, werd geïmplementeerd met de Doorbraakmethode. Dertien multidisciplinaire teams participeerden, met in totaal 101 zorgprofessionals en 536 patiënten. Het beloop van de depressiesymptomen en de behandelresponse werden gemeten aan de hand van de Beck Depression Inventory (BDI) totdat herstel werd bereikt; herstel werd gedefinieerd als een BDI-score van 10 of lager gedurende een periode van 6 maanden.

Tweederde van de patiënten (66%; n=356 patiënten) had een niet-ernstige depressie. Het percentage van patiënten met een niet-ernstige depressie die werden behandeld volgens het stepped-care model was gemiddeld 78% (range 53-100%). Significant meer patiënten met een niet-ernstige depressie ontvingen de eerste-stap behandeling naarmate het project vorderde. In de groep met een ernstige depressie werd 57% (range 25-100%) van de patiënten behandeld conform het stepped-care model. De overige 43% van deze patiënten werd onderbehandeld en ontving te lichte interventies, in plaats van psychotherapie dan wel antidepressiva. Blijkbaar volstaat de implementatiemethode niet voor de groep patiënten met een ernstige depressie. Sleutelvariabelen in de veranderstrategie, die worden beschreven in relatie tot de uitkomsten op mesoniveau, zijn: top-down doelstellingen, het aanbieden van praktische tools, standaarden en duidelijke instructies over de gevraagde gedragsverandering van zorgprofessionals - om te onderscheiden naar ernst van de depressie en om minder intensieve interventies aan te bieden - en het objectief meten van uitkomsten met de

BDI. De geïntroduceerde gedragsverandering werd bestendigd gedurende de veranderperiode en in de meeste aan het onderzoek deelnemende teams ook na deze periode.

We concluderen dat een stepped-care benadering aannemelijk is voor patiënten en voor zorgprofessionals, en kan leiden tot kwaliteitsverbetering van de depressiezorg.

6 Een zelfhulpinterventie voor comorbide depressie en angststoornissen in de diabeteszorg

Zelfhulpinterventies kunnen een gepaste eerste stap zijn in de behandeling van een depressie of angststoornis die optreedt bij patiënten met diabetes mellitus type 2. Strategieën voor tijdige herkenning en adequate behandeling van de psychische aandoening zijn belangrijk bij deze patiënten. Dit hoofdstuk laat zien dat een zelfhulpinterventie succesvol geïmplementeerd en geïntegreerd kan worden in de diabeteszorg, vanuit een chronische-zorgbenadering, met als doel onderherkenning en onderbehandeling van psychische aandoeningen te voorkomen. De interventies vragen een minimale inzet van diabetesverpleegkundigen om, aan de hand van hiertoe ontwikkelde tools, de screening uit te voeren, de zelfhulpinterventie aan te bieden en te begeleiden, of de patiënt te verwijzen voor meer gespecialiseerde zorg. De verpleegkundigen werken samen met de patiënt en de huisarts.

Gedurende de pilot-studie met pre-test post-test design screenden zeven getrainde verpleegkundigen die samenwerkten met 73 huisartsen, 111 diabetes type 2-patiënten middels een gestandaardiseerd screeningsinterview. Zesentwintig van de 53 screenpositieve patiënten voldeden aan de diagnostische criteria voor een angststoornis of depressieve stoornis volgens het MINI International Neuropsychiatric Interview. Van deze 26 patiënten volgden er 16 de zelfhulpinterventie in vijf sessies. Na zes maanden vond follow-up meting plaats. Een procesevaluatie vond plaats halverwege de training en aan het einde van de pilotstudie.

Gemeten met de Patient Health Questionnaire (PHQ), verbeterden angstsymptomen (3.2 punten verbetering; p=0.011), depressiesymptomen (5.7 punten verbetering; p=0.007), en ernst van de somatische symptomen (2.9 punten verbetering; p=0.041) significant. Diabetes-gerelateerde negatieve emoties (op de PAID-NL) verminderden met 3.8 punten (p=0.048). De zelfgerapporteerde algehele gezondheidsstatus gemeten met de Visual Analogue Scale (range 0-100) van de EQ-5D, verbeterde gemiddeld met 14 punten (p=0.007). Emotioneel rol-functioneren (SF-36) liet 33.4 punten verbetering zien (p=0.010), fysiek rol-functioneren verbeterde met 40 punten (p=0.007) en emotioneel welbevinden met 19.4 punten (p=.003). Depressie- en angstsymptomen verminderden, net als diabetes-gerelateerde distress, na het volgen van de begeleide zelfhulpinterventie,

terwijl het gezondheidsprofiel en de mentale component van kwaliteit van leven verbeterden.

Deze bevindingen suggereren dat de verbeterstrategie op het mesoniveau van de zorg, bestaande uit het implementeren van zelfmanagementstrategieën begeleid door de verpleegkundige en het bieden van praktische tools voor verpleegkundigen, resulteert in verbeterde patiëntenuitkomsten. De getrainde verpleegkundigen waren competenter in het screenen en behandelen van emotionele problemen bij diabetespatiënten, als deze gefaciliteerd werden met een gevalideerde vragenlijst en tools voor het begeleiden van de zelfhulpinterventie. Nauwe betrokkenheid van de huisartsen lijkt een relevante factor in het accepteren van deze rol van de verpleegkundige.

III De effectiviteit van depressiezorg-management en de kostenutiliteit van stepped care

In deel III worden achtereenvolgens de effectiviteit van depressiemanagement en de kostenutiliteit van stepped care geëvalueerd. Om de heterogeniteit in uitkomsten van depressiemanagement-programma's te kunnen verklaren werd een systematische review van reviews en empirische studies verricht, inclusief metaregressie-analyses.

Om de positieve bevindingen in deel II verder te onderzoeken werd evidentie vanuit verschillende bronnen gecombineerd in een modelleringsstudie.

7 De effectiviteit van depressiemanagement-programma's

In dit hoofdstuk worden de meta-analyse en metaregressie-analyses over effectstudies naar programma's voor depressiemanagement vanuit het chronische-zorgmodel besproken. De meta-analyse laat zien dat de depressiemanagement-programma's over het algemeen effectief zijn. Gepoolde effecten van deze zorgprogramma's lieten, in vergelijking met gebruikelijke zorg, significante verbetering zien in response op de behandeling (RR=1.38; p<0.05) en adherentie aan de behandeling (RR=1.36; p<0.05). De resultaten over de kosten waren beperkt en minder overtuigend. Het is vooralsnog onduidelijk welke specifieke interventies of componenten van deze programma's essentieel zijn in het bewerkstelligen van effectiviteit.

Aan de hand van metaregressie-analyses is onderzocht in welke mate de geobserveerde heterogeniteit die gerelateerd is aan de effectiviteit van de depressiemanagement-programma's, kan worden verklaard door kenmerken van de geïncludeerde studies (kwaliteit van de studies, follow-up duur), het aantal

componenten in het chronische-zorgmodel, en patiëntkenmerken. Subgroep-analyses lieten een aantal significante verbeteringen zien die werden getest door metaregressie-analyses.

Studiekwaliteit verklaarde in relatie tot verbetering van de behandelresponse (RR=1.39; 95% CI: 1.12-1.73; I^2=88% in de subgroep-analyse), een substantieel deel van de heterogeniteit (36.6%; p=0.04). Subgroep-analyse van patiëntkenmerken liet zien dat de effectiviteit van de depressiemanagement-programma's voor patiënten met een depressieve stoornis minder groot was (RR=1.24; 95% CI: 1.09-1.41; I^2=36%) dan voor patiënten met depressiesymptomen waarbij niet werd voldaan aan de diagnostische criteria (RR=1.88; 95% CI: 1.46-2.42; I^2=0%). In de meta-regressie-analyse verklaarde het hebben van een depressieve stoornis (in plaats van depressiesymptomen waarbij niet wordt voldaan aan de criteria van een depressieve stoornis), een substantieel deel van de heterogeniteit in de adherentie aan de behandeling (88.7%; p=0.01). Mogelijke redenen hiervoor zijn dat het moeilijker is voor patiënten met een depressieve stoornis om therapietrouw te zijn aan de behandeling, of dat het er aan ligt dat de gepaste interventie intensiever is, of dat het voor hulpverleners moeilijker is om de behandeling uit te voeren zoals bedoeld. Duidelijk is dat het de moeite loont om therapietrouw van de patiënt en adherentie van de zorgprofessional te verbeteren, aangezien dit bijdraagt aan het vergroten van de effectiviteit van depressiemanagement-programma's.

Deze studie onderstreept dat het effectief is om in depressieprogramma's rekening te houden met de ernst van de depressie, en andere bronnen van heterogeniteit, en dat dit bijdraagt aan persoonsgerichte zorg. Andere aspecten van klinische diversiteit, zoals comorbiditeit, persoonlijke geschiedenis, levensfase en andere patiëntkenmerken dienen nader onderzocht te worden als bron van heterogeniteit, want indien deze factoren de heterogeniteit in uitkomsten van de zorg kunnen verklaren, is het relevant om de zorg hierop gerichter af te stemmen.

8 De kostenutiliteit van richtlijnconforme stepped-care algoritmes

Klinische richtlijnen voor depressieve stoornissen bevelen stepped-care strategieën aan voor het sequentieel inzetten van evidence-based behandelingen, die bij voorkeur kosteneffectief zijn. In dit hoofdstuk wordt de kostenutiliteit van op de Multidisciplinaire richtlijn Depressie gebaseerde stepped-care algoritmes geëvalueerd aan de hand van een depressie state-transition model, een adaptatie van het model van Vos et al. (2005). Dit economische model maakt een onderscheid naar lichte versus matige tot ernstige depressieve stoornissen. De inputwaarden in het model zijn gebaseerd op literatuuronderzoek en op de expertschattingen door de leden van de Werkgroep Richtlijnontwikkeling Multidisciplinaire richtlijn Depressie. Stepped-care scenario's werden vergeleken met care-as-usual scenario's.

We simuleerden het zorggebruik van een patiëntenpopulatie met verschillende ernstniveaus van de depressie, de bijbehorende kosten van de zorg en opgeleverde gezondheidswinst, uitgedrukt in voor kwaliteit van leven gecorrigeerde

levensjaren (QALY's). De modelleringsstudie laat zien dat het bereiken van gezondheidswinst aan de hand van de stepped-care algoritmes hoogstwaarschijnlijk kosteneffectief is. De modelsimulaties geven aan dat één QALY gezondheidswinst bij een lichte depressieve stoornis in het stepped-care scenario samengaat met een kostenpost van € -2.500 (dominant), in vergelijking met care-as-usual. De kosten zijn € 3.200 per QALY bij een matige tot ernstige depressieve stoornis.

Bij een willingness-to-pay plafond van € 20.000 voor het winnen van een extra QALY, kunnen de beide stepped-care algoritmes als kosteneffectief worden beschouwd, met meer dan 95% zekerheid. Dit betekent dat stepped care zeer waarschijnlijk een kosteneffectieve keuze is vergeleken met care-as-usual. Deze bevindingen ondersteunen de Nederlandse richtlijnaanbevelingen, volgens welke de stepped-care algoritmes de klinische besluitvorming ondersteunen.

9 Algemene discussie

In hoofdstuk 9 tenslotte, de algemene discussie, worden de voornaamste bevindingen besproken, in antwoord op de uitgangsvragen en in het licht van recente studies. Ook worden theoretische en methodologische overwegingen, beperkingen van de uitgevoerde studies en implicaties van de bevindingen besproken. De volgende aanbevelingen worden gegeven voor onderzoek, beleid en praktijk van de depressiezorg.

1 *Maak een onderscheid tussen stepped care als behandelstrategie en stepped care als wijze van organiseren van de zorgverlening.*

Doe dit zowel in onderzoek als in de toepassing van stepped care in zorgbeleid en praktijk van de depressiezorg. Algemene conclusies in de evaluatie van stepped care kunnen alleen onder voorbehoud worden gemaakt indien slechts één aspect ervan is onderzocht. Onderzoek hoe zorgprofessionals werken met de heuristieken voor klinische besluitvorming, in klinisch redeneren en in gedeelde besluitvorming, en hoe zij omgaan met onzekerheid.

2 *Laat de stappenvolgorde van interventies aansluiten op de aanbevelingen in de Multidisciplinaire richtlijn Depressie.*

Doe dit bij het opzetten van onderzoek en implementatie, bij het toepassen van stepped-care behandelstrategieën en bij het organiseren van de depressiezorg. Dit geldt voor het overwegen van verschillende interventies binnen een behandelstap, de volgorde waarin interventies elkaar kunnen opvolgen en de criteria voor evaluatie en overstappen op een vervolginterventie. Dit betekent ook dat, bij voorkeur, interventies voor het gehele zorgcontinuüm voorhanden zijn, inclusief interventies die als eerste stap worden ingezet, maar ook gespecialiseerde interventies voor persisterende, terugkerende of meer ernstige depressie.

3 *Zorg dat het sturingsprincipe in de zorg is ingegeven door de relevantie voor het kunnen bijstellen van individuele behandelstrategieën.*

Kies bij het monitoren en evalueren van zorgprocessen op het mesoniveau van de zorg, de indicatoren en metingen zodanig dat deze aansluiten op kritische beslispunten en behandeldoelen in de individuele patiëntenzorg. Op deze wijze kunnen te registreren proces- en uitkomstendata dienen als sturingsinformatie in stepped-care behandelstrategieën en kunnen behandeluitkomsten voor patiënten worden verbeterd. Zorg dat kwaliteitsindicatoren voor extern en intern gebruik op elkaar aansluiten, ook bij kwaliteitscontrole, zorgcontractering en het maken van zorgovereenkomsten of andere prestatieafspraken. Zo kan een verbetercyclus op basis van deze sturingsinformatie de kwaliteit en efficiëntie van zorgprocessen verbeteren.

4 *Gebruik de zorgstandaard en de richtlijnen voor diagnostiek en behandeling waarvoor deze zijn ontwikkeld.*

Zorgstandaarden, die zijn gebaseerd op richtlijnen, kunnen richtlijnen niet vervangen of overbodig maken, want deze verschillende kwaliteitsstandaarden dienen andere doelen. Verbetering van de kwaliteit en efficiëntie van de depressiezorg kan worden gebaseerd op de zorgstandaard, die is ontwikkeld door alle betrokken zorgpartijen. Dit kan alleen indien deze wordt gebaseerd op actuele, regelmatig geactualiseerde richtlijnen voor goede zorg, die worden ontwikkeld om zorgprofessionals te ondersteunen in het nemen van beslissingen over het beste behandelbeleid en gezamenlijke besluitvorming met de patiënt.

5 *Pas op de richtlijnen gebaseerde stepped-care behandelstrategieën toe bij persoonsgerichte zorg.*

Onzekerheid is inherent aan de diagnostiek en behandeling van depressie en hiermee dienen patiënten en zorgprofessionals rekening te kunnen houden. Om zorgprofessionals te ondersteunen bij beslissen in onzekerheid zijn de stepped-care algoritmes van toegevoegde waarde, zolang evidentie voor matching-factoren waarmee differentiële effecten kunnen worden bereikt – en die voorafgaand aan de behandeling te herkennen zijn – gering is. Ontwikkel ook heuristieken voor patiënten, zoals actuele en beslissingsondersteunende keuzehulpen, die hen niet alleen informeren over passende zorg, maar ook kunnen voorbereiden op gedeelde besluitvorming. Deze keuzehulpen dienen rekening te houden met beslissingsonzekerheid en met patiëntenvoorkeuren.

10 Conclusies

In dit proefschrift verkennen we de toepasbaarheid en kostenutiliteit van stepped-

care strategieën voor depressie en wat de toegevoegde waarde hiervan is voor de depressiezorg. Stepped-care behandelstrategieën kunnen zorgprofessionals, en hun patiënten, ondersteunen bij het nemen van beslissingen in onzekerheid, waarbij zowel overbehandeling als onderbehandeling wordt voorkomen. Een stepped-care zorgverlening kan bijdragen aan het reduceren van deze onzekerheid en de kwaliteit van zorgprocessen verbeteren, zoals uitgelegd in dit proefschrift. Dit proefschrift draagt bij aan de evidentie voor de toepasbaarheid, aannemelijkheid, effectiviteit en kostenutiliteit van stepped-care strategieën voor depressie.

De voornaamste conclusies van dit proefschrift voor beleidsmakers en zorgprofessionals zijn, ten eerste, dat stepped-care strategieën essentieel zijn in het verkrijgen van optimale behandelresultaten voor depressie-patiënten. En ten tweede, bij kwaliteitsverbetering op het meso- en macroniveau van de zorg is het van cruciaal belang dat de focus ligt op het primaire proces en het bereiken van verbeterde uitkomsten op patiënten-niveau. Beleidsmakers in de zorg kunnen de depressiezorg verbeteren door de voorwaarden te scheppen om stepped-care strategieën uit te kunnen voeren. Zorgprofessionals kunnen de behandeluitkomsten voor patiënten verbeteren door beslissingsondersteunende instrumenten, zoals de stepped-care algoritmes, te gebruiken bij beslissingen in onzekerheid.

Stepped care draagt bij aan het leveren van zorg op maat vanuit een persoonsgerichte benadering. Zolang dit het geval is geldt *voor elke casus*, dat de stepped-care benadering waarde toevoegt in de zorg voor depressie.

Dankwoord | Acknowledgements

Dankwoord

Het schrijven van dit proefschrift - in combinatie met het werk voor het Trimbos-instituut en voornamelijk in vrije tijd - heeft veel verdieping gebracht in mijn werkzame leven. Dankbaar ben ik voor alle aanmoediging, prettige samenwerking en ondersteuning die dit mogelijk heeft gemaakt. Als dit proefschrift eerder gereed was geweest, dan was het een ander proefschrift geworden en was ik een ander persoon.

Mijn grote dank aan ieder die heeft bijgedragen aan het tot stand brengen van dit proefschrift: aan alle deelnemende patiënten en hulpverleners in de verschillende studies en aan de opdrachtgevers voor het mogelijk maken van deze studies; aan alle werkgroepleden, adviesgroepleden, programmahoofden en projectgroepleden voor hun belangrijke bijdragen en de constructieve samenwerking; en aan alle experts, beleidsmakers, ervaringsdeskundigen, collega-onderzoekers en collega's die mijn hun wijze raad en waardevolle advies gaven. In het bijzonder wil ik graag de volgende personen bedanken.

In de eerste plaats veel dank aan mijn beide promotoren, Professor Ton van Balkom en Professor Filip Smit. *Beste Ton,* mijn grote dank voor de jarenlange fijne samenwerking rondom de 'levende' multidisciplinaire richtlijnen voor angststoornissen en voor depressieve stoornissen, waardoor wij behalve op deze richtlijnen konden bouwen op elkaar, bij het werk voor dit proefschrift en alles wat dit met zich meebracht. Zeer veel dank voor de ruimte die je hebt gegeven mijn eigen tempo te volgen in het werken aan dit proefschrift, voor alle geruststelling en begrip wanneer andere prioriteiten in het werk of in het leven op de voorgrond traden, en voor alles dat wat jou betreft misschien vanzelfsprekend lijkt maar zo helemaal niet voor de hand liggend is. En ook heel veel dank voor al je inhoudelijke bijdragen, je altijd opbouwende commentaar en feedback en je besliskracht en richtinggevende pragmatisme waar dit nodig was. Ik heb veel van je geleerd, zeker ook in de afrondende fase. Het is een voorrecht jou als promotor te mogen hebben en ik hoop onze samenwerking nog lange tijd te kunnen voortzetten.
Beste Filip, voor altijd ben ik je dankbaar dat je mij destijds, in mijn afstudeerjaar tijdens een promotiereceptie aan de vakgroep, aanraadde om bij het Trimbos-instituut, waar jij toen al werkte, een open sollicitatiebrief in te sturen. Ik vind het heel bijzonder dat je jaren later mijn promotor werd. Veel dank voor je grote behulpzaamheid en hoffelijkheid gedurende de jaren. De mooiste herinnering heb ik aan de cursus over Markov-modellering die we samen in Brussel volgden, in de periode dat jij nog aan jouw proefschrift werkte. Je grote kennis van onderzoeksmethoden en snelle vermogen tot grondige verdieping in een nieuwe aanpak of methode, kwamen goed van pas bij de modelleringsstudie voor dit proefschrift. Ik ben je heel erkentelijk voor je kritische en zorgvuldige commentaren en meedenken bij het tot stand brengen van dit proefschrift. Ik hoop dat we nog lang collega's zijn en zie uit naar de tijd dat we weer meer over chimpansee-onderzoek, concertbezoek, verre reizen of fotografie zullen praten.

Aan de voorzitter en de leden van de Promotiecommissie, Professor Aartjan Beekman, Professor Bea Tiemens, Professor Annemiek van Straten, Dr. Leona Hakkaart-van Roijen, Professor Aart Schene en Professor Silvia Evers – heel veel dank voor alle getoonde interesse voor dit proefschrift, voor de betrokkenheid bij het onderwerp en voor het lezen en beoordelen van het manuscript. Ik vind het een eer dat ieder ook als opponent aanwezig zal zijn tijdens de proefschriftverdediging.

Beste Aartjan, bovendien veel dank voor je belangstelling voor mijn voortgang wanneer we elkaar tegenkwamen en ook voor de heldere en vernieuwende presentaties die je destijds op het Trimbos-instituut hield over de behandeling van depressie en het bereik van evidence-based interventies.

Beste Bea, je stond aan de start van de eerste studie over stepped care bij depressie in Nederland. Ik herinner me hoe het onderwerp onmiddellijk mijn interesse wekte. En hoe blij ik was dat de kans zich voordeed hierop te mogen werken toen jij mij betrok in jouw projectgroep. Met begrip natuurlijk, maar ook met weemoed denk ik eraan terug dat jouw carrièrestap inhield dat wij vanuit het Trimbos-instituut zelf het project moesten afmaken. Ik ben verheugd en vereerd dat je in deze afrondende fase opnieuw ten zeerste betrokken bent, als lid van de Promotiecommissie.

Beste Annemiek en beste Leona, de eerste kosteneffectiviteitsstudie op het gebied van stepped care versus matched care voor depressie in Nederland voerden jullie uit. Ik bewonder jullie academische aanpak (en Annemiek, die viel al op toen wij nog kamergenoten waren op het Trimbos-instituut!). Veel dank ervoor dat jullie mij destijds betrokken in de werkconferentie en publicatie over de betekenis van de bevindingen voor de praktijk en het beleid in de Nederlandse depressiezorg. Ik vind het heel leuk dat jullie allebei, als leden van de Promotiecommissie, een belangrijke rol hebben bij mijn proefschrift.

Beste Aart, op het gebied van kwaliteitsontwikkeling en kwaliteitsstandaarden in de ggz kunnen jouw inzichten richting geven. Veel dank voor je betrokkenheid vanuit de Promotiecommissie!

Beste Silvia, dat je er getuige van was toen ik vernam dat het manuscript was goedgekeurd door de Leescommissie en we dit samen vierden, op het lolaHESG congres dit voorjaar, was voor mij heel leuk en bijzonder. Ik ziet uit naar een verdere kennisuitwisseling en samenwerking als collega's van het Trimbos-instituut.

Veel dank aan de leden van de Werkgroep Richtlijnontwikkeling Multidisciplinaire richtlijn Depressie en de Werkgroep Zorgstandaard Depressieve stoornissen – voor de intensieve samenwerking, voor de levendige uitwisseling over het praktijkveld en voor het gevoel van saamhorigheid in de context waarin richtlijnontwikkeling plaatsvindt. In het bijzonder veel dank aan Jan Spijker, Claudi Bockting, Irene van Vliet, Eric Ruhé, Sako Visser, Harm van Marwijk, Mariëlle van Avendonk, Sonja Aalbers, Anneke Huson, Marlies Oudijk en Nathalie Kelderman.

Beste Claudi, veel dank voor de verbindingen die je altijd legt en de inspiratie die dit geeft, met bewondering voor je expertise. Ook veel dank aan de Trimbos-collega's van Zorginnovatie: aan Nelleke van Zon en Angita Peterse voor de

jarenlange ondersteuning op deze projecten, aan Daniëlle van Duin en Matthijs Oud van het kernteam evidence-based richtlijnontwikkeling voor alle afstemming en kennisuitwisseling en aan Marja van Bon en Henny Sinnema voor de goede samenwerking voor de zorgstandaarden.

Het werken aan de artikelen betekende dat er altijd een auteursgroep was die mij omringde. Veel dank hiervoor, behalve ook aan mijn promotoren, aan alle coauteurs: Marianne Donker, Jan Spijker, Claudi Bockting, Talitha Feenstra, Erik Buskens, Matthijs Blankers, Lidwien Lemmens, Karin Lemmens, Bert Vrijhoef, Lotte Steuten, Hanneke Drewes, Caroline Baan, Arianne Elissen, Gerda Holleman, Siska de Jong, Jasper Nuijen, Christina van der Feltz-Cornelis, Gerdien Franx, Jochanan Huyser, Jacomine de Lange, Henny Sinnema, Anna Muntingh, Harm van Marwijk en Paul Rijnders. *Beste Jan*, van alle coauteurs schreef ik met jou mijn meeste publicaties. Speciale dank hiervoor! *Beste Bert,* veel dank voor het bij elkaar brengen van onze heel productieve auteursgroep op het gebied van chronische-ziektemanagement. *Beste Lidwien,* ik heb heel fijne herinneringen aan onze samenwerking destijds, tijdens mijn uitgebreide kraamverlof, waarbij jij Rutger's ritme van voedingen en slaapuurtjes helemaal kende om op de geschikte tijdstippen te bellen voor de afstemming over onze meta-review. Je bent een top-coauteur! *Beste Talitha,* veel dank voor alle goede uitleg en aanwijzingen bij mijn inwijding in de gezondheidseconomie. Aan Pieter van Baal en Steef Redeker – veel dank voor de bespreking van de economische evaluatie tijdens het lolaHESG-congres, met dank aan de goede programmering door Talitha Feenstra. *Beste Pieter,* na jouw hulp bij de programmering van het economische model en de eerste analyses werd hiermee de cirkel rond. Veel dank!

Het Trimbos-instituut is een fantastische plek om te werken. Veel dank hiervoor aan de oud- en nieuwe bestuurders van het Trimbos-instituut, in het bijzonder oud-bestuurders Marianne Donker en Jan Walburg. *Beste Marianne,* veel dank voor je vertrouwen in mijn kunnen, in mijn beginjaren bij het Trimbos-instituut en bij aanvang van het promotietraject dat tot dit proefschrift zou leiden. *Beste Jan,* veel dank voor de TOP-tijd en alle kansen die je me toevertrouwde bij de internationale oriëntatie en het opbouwen van het World Health Organisation Collaborating Centre for dissemination of good practices in mental health. Veel dank aan alle enthousiaste, betrokken en behulpzame collega's, van de niet al genoemde collega's in het bijzonder aan: Aafje Knispel, Anneke van Wamel, Agnes van der Poel, Annemiek Mutsers, Daniëlle Branderhorst, Daniëlle Meije, Esther Croes, Hans Kroon, Harry Michon, Ionela Petrea, Ireen de Graaf, Jasper Nuijen, Joran Lokkerbol, Joris Staal, Karin Monshouwer, Laila Zaghdoudi, Laura Shields, Linda Bolier, Margriet van Laar, Marijke de Groot, Marjan Heuving, Margreet ten Have, Nancy van Baggem, Ninette van Hasselt, Rianne van der Zanden, Robert Vermeulen, Ron de Graaf, Saskia Allema, Ton Kaljee en Wilma Boevink en aan Marieke Ten Kortenaar en Jan te Brinke van de Canon studio en repro. En last but not least aan Annemarie Pijnappel-Kok, Nathalie Dekker, Eva Ehrlich, Monique Croes en het hele team Publieksinformatie voor de positieve sfeer op de kamer, in de gang en met het team.

Beste Annemarie, het is zo fijn om dit proefschrift te kunnen afronden en tegelijkertijd samen iets nieuws te kunnen opbouwen – bedankt hiervoor en voor alle ruimte die je geeft!

Veel dank aan de Faculteit der Geneeskunde, Vakgroep Psychiatrie, Amsterdam UMC, Vrije Universiteit Amsterdam en aan GGZ InGeest, onderzoek & innovatie – voor alle ondersteuning bij het realiseren van dit proefschrift.

Veel dank aan Korinna van Balkom voor de mooie vormgeving van dit proefschrift – "A designer knows perfection is achieved, not when there is nothing more to add, but when there is nothing left to take away" (Antoine de Saint-Exupery).

I sincerely thank Professor Ed Wagner, Professor Michael Von Korff, Stacey Chantker Shapiro, Dr. Robin Dea, Meike van Ginneken, Dr. Josep Manel Picas, Dr. Matt Muijen, Geoff Huggins, Professor Glyn Elwyn and Professor Jack Dowie – for their personal notes, kind and valuable comments during conferences or working visits, over the years, that sharpened my thoughts.
Veel dank aan Professor Monique Smeets en Professor Cilia Witteman – voor de kennis die zij ook na mijn studietijd bij Psychonomie overbrachten.

At this point, I wish to thank primatologist, nature conservationist and UN Messenger of Peace Dr. Jane Goodall. *Dear Jane,* I am grateful for all your inspiration throughout the years. Thank you for sharing your sharp observations and judgmental and non-judgmental thoughts. Thank you truly for making the exceptional normal and making the normal phenomenal. And many thanks to all the inspiring people that I met through you, or through the Jane Goodall Instituut Nederland. To social antropologist and wildlife conservationist Saba Douglas-Hamilton. *Dear Saba,* here is to you for reminding me every year, in person or via Roy, that you can do it all, as long as you don't have to do it all at the same time. And a warm thank you to economist Professor Noreena Hertz. *Dear Noreena,* thank you for letting me in your circle, when you were a Visiting Professor in Utrecht and when you invited me over while I was in London for a NHS conference, and for sharing your academic and broader view and the inspiration you brought with your world changing talks.

Speciale dank aan Tineke Meulenkamp & Dennis Janssen, Lyna Degen-Polikar & Steven Degen, Agnes Verkerk, Thea van Zoelen, Heleen Maurice-Stam, Margriet van Laar, Michiel Cornelissen, Wendy Schuurman, Anat Zuriel, Marieke Vriezen-Kremers, Andra Herngreen en Peter Spithout – voor de gouden vriendschap. En aan Mirjam Valk, Jeroen Kerseboom en Hazel Hull – for old times' sake. A special thank you to Rosalind Rosenberg – for her hospitality and for driving me around Washington D.C. in her open cabrio. And many thanks to Larry Prager – for his language support. Aan Christa & Joost, Elke & Willem, Marlotte & Maarten, Erica & Matthijs, Candice & Dirk-Jan, Kim & Bardo, Janneke & Marc – voor alle gezelligheid rondom de speelafspraken van de kinderen en de extra tijd waarmee ik soms enorm geholpen was!

Lieve Tineke, bijzondere dank voor je trouwe vriendschap al sinds de introductiedagen Psychologie, met veel bewondering voor je kracht en kunnen. We hebben samen al veel beleefd en het wordt weer tijd voor nieuwe ervaringen!
Lieve Lyna, sinds we elkaar leerden kennen als kamergenotes hebben we al zoveel gedeeld. Veel dank voor alles wat het werk interessanter maakt en ook voor alle feestjes en versiering, je stijl en goede smaak!
Wat fijn, Tineke en Lyna, dat jullie als paranimfen aan mijn zijde zullen staan.

Lieve familie en schoonfamilie, bedankt voor alle warmte, gezelligheid en betrokkenheid. *Lieve Paul*, jouw gevleugelde uitspraak "Geniet van het leven!" zal ik niet vergeten. *Lieve Josien*, Seguirijas vind ik de mooiste dans, maar Alegrías zie ik jou het liefste dansen! *Lieve Anne en Louise,* ik geniet ervan jullie te zien opgroeien. Jullie kunnen alles!
Lieve Erik, wat ben ik blij dat jij mijn broer bent en dat we zulke fijne herinneringen hebben om te delen. Dank je wel voor je snelle en scherpe inzichten en bruikbare adviezen wanneer ik die best kan gebruiken. Zo doe ik toch altijd weer net als mijn grote broer! Zelfs ook iets met wiskundige overgangskansen en reeksen, het optimaliseren van sequenties en het belang van feedbackinformatie!
Aan mijn ouders – heel veel dank voor jullie liefde en aanmoediging, die alles mogelijk maken. En voor alle praktische ondersteuning en gezelligheid, waardoor alles makkelijker gaat. En voor zoveel meer! *Lieve Papa,* de brede interesse en ook de accuratesse, het geduld en doorzettingsvermogen, die nodig waren om dit proefschrift te schrijven, heb ik van jou! Veel dank voor je wijsheid, goede ideeën en de inspiratie die dit geeft. *Lieve Mama,* voor de benodigde ijver, doelgerichtheid, zorgvuldigheid en toewijding, heb ik jou als goed voorbeeld! Heel veel dank hiervoor en voor al je inspirerende, wijze woorden en ook voor alle relativering. Bedankt voor alles!
Lieve Roy, je bent er altijd voor mij en voor jou hoef ik geen proefschrift te schrijven. Hoe dankbaar ik je hiervoor ben, en voor zo veel meer, is niet in woorden uit te drukken. Als het er op aan komt zijn we samen sterk, zoals we al hebben laten zien – dit is zo fijn om zeker te weten! Alles wat we samen hebben gedaan en meegemaakt is door jou zoveel leuker, relaxter, beter en mooier. Wat zullen we eens gaan doen met alle verworven vrijheid?!
Mijn lieve Rutger, het meeste werk voor dit proefschrift is verricht tijdens je slaap- en schooltijden, speel- en feestafspraken. Dat je zo helpend zou zijn in de eindspurt, zoals met alle wifitechnische ondersteuning, door het hele huis en waar we ook waren, had ik niet eerder kunnen bedenken. Volg je hart en blijf jezelf want dat is, mét alle geluk van de wereld die ik je wens, nodig en genoeg om je dromen te verwezenlijken en te bereiken wat je wenst! Dank je wel voor alle verrijking die je brengt in ons leven. Van jou leer ik het meest!

Jolanda Meeuwissen
Utrecht, 30 augustus 2018

Curriculum Vitae

Curriculum Vitae

Jolanda Antonia Cornelia Meeuwissen was born on November 12, 1971, in Borsele, in the province of Zeeland, The Netherlands. Jolanda was raised in Goes where she attended the unified pre-university education (ongedeeld VWO) of the St. Willibrord College (now Ostrea Lyceum) from 1984 to 1990. Jolanda studied Psychology at Utrecht University from 1990 to 1996, receiving her propaedeutic diploma in 1991. In 1996, she graduated with a Master of Science degree in Psychology at the Department of Psychonomics and at the Department of Clinical Psychology and Health Psychology. Jolanda was awarded the Primary Certificate of the Albert Ellis Institute for Rational Emotive Behavior Therapy in 1998.

Since 1997, after an introduction by Professor Filip Smit, Jolanda has been a research associate at the Trimbos Institute, the Netherlands Institute of Mental Health and Addiction, in Utrecht, working in positions from junior to senior researcher. From 2001 to 2005 she attended courses in health services, health technology assessment, and research methods at the EMGO+ Institute for Health and Care Research and at the Erasmus MC Netherlands Institute for Health Sciences (NIHES). Thereafter she learned and participated in network meetings on evidence-based guideline development, such as the Guidelines International Network (GIN), the HARING-project, and the Dutch GRADE Network. In 2018, Jolanda became a member of the Society for Medical Decision Making and a member of EACLIPT, the European Association of Clinical Psychology and Psychological Treatment.

Jolanda conducted nearly 100 projects commissioned by the Ministry of Health, Welfare and Sport, ZonMw (the Netherlands Organization for Health Research and Development), GGZ Nederland (the Dutch Association of Mental Health and Addiction Care), professional associations, client organizations, and other health organizations, such as the World Health Organization Europe. The studies presented in this PhD thesis were based on several of these projects.

Jolanda is regularly invited to advise in external care quality projects, speak at (international) congresses and courses for continuing education, and to peer-review journal articles and application grants. As a project leader and researcher, Jolanda contributes to the development, implementation, and evaluation of mental healthcare models, programmes and interventions, clinical guidelines and quality standards to improve mental health care, as well as instruments to support decision making on the diagnostics and treatment of mental disorders. Recent projects include the development of multidisciplinary care standards for anxiety disorder and depressive disorder, multidisciplinary guidelines for mood disorders in children and for the children of parents with a mental disorder, and quality standards for nursing care in the area of somatic screening, lifestyle promotion, and sleeping disorders.

Several of Jolanda's ongoing projects focus on the current maintenance of the multidisciplinary guidelines for depressive disorder and for anxiety disorder, thereby providing the evidence basis underlying the studies described in her PhD thesis. The valuable cooperation of Professor Ton van Balkom, chair of the Guideline Development Group in these projects, enabled the accomplishing of this academic dissertation at the Department of Psychiatry of the Amsterdam UMC, VU University, Amsterdam.

Jolanda is happily married to photographer Roy Borghouts and the proud mother of Rutger, their 9-year-old son.

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Dissertation series

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Today's topics in mental health care concern finding solutions for providing good patient care with a perceived scarcity of resources in the face of growing financial and administrative pressures and increasing caseloads. The current way of organising depression care may not always lead to the best treatment for patients.

This PhD thesis presents an approach to support care professionals in improved clinical decision making with stepped-care heuristics that reduce uncertainty around the prognosis and progression of depression, while avoiding both over-treatment and under-treatment in individual treatment strategies. This thesis also addresses quality improvement in depression care through stepped-care service delivery with care improvement strategies from a chronic care management approach.

With the aim of advancing depression care for the direct benefit of all patients, Jolanda Meeuwissen explores the applicability and cost-utility of stepped-care strategies. The findings and implications resulting from the studies in this thesis may serve the care debate on healthcare policy and practice related to these issues.