General Introduction
General introduction:

The subject of the thesis you have just started to read is depression, a commonly encountered mental health disorder. Patients in the Netherlands who are depressed and seek help for this condition will nearly always consult their General Practitioner (GP) first before seeing a psychologist, psychiatrist, or another mental health specialist. This is not always an easy task for GPs, the 'gatekeepers' in our health care system.

What it means to be clinically depressed is the topic of the first section of this introduction. The problems experienced by GPs in the process of diagnosing and treating depression are discussed in the second section. The third section introduces collaborative care, a model that may provide an effective approach to dealing with some of the obstacles to effective treatment of depression in primary care.

In everyday practice depression and physical symptoms (such as pain or dizziness) commonly co-occur. This is why an important sub aim of this thesis was to explore the influence of physical symptoms on the course of MDD and treatment effectiveness for this disorder. More information on this can be found in the sixth section of this introduction.

1. What is this thing called depression?

The general public often associates depression with feeling blue or with the effect of a stroke of bad luck. It is very tempting to 'help' someone who feels depressed by saying: "Cheer up, everyone feels blue from time to time. Just have a nice long walk in the park and watch a nice movie afterwards. You'll feel fine again in no time." Although this is good advice for most people, it will probably not help those who are suffering from a severe depression in the clinical sense of the word. For many people suffering from clinical depression the concept of 'a nice long walk in the park' would feel pretty much like asking them to undertake Frodo's odyssey to Mount Doom.

The first step during the quest of treating depression is the diagnosis. But this is where analogies with the quest in Lord of the rings must stop. Depression is not something you can 'hold' like a ring. It is not as easily diagnosed (or treated) as for instance a bone fracture. Diagnosing depression is somewhat more intuitive and is partly based on the experience of the clinician. Lab results do not provide a discriminative test. Nevertheless criteria have been established over the years. When clinicians talk about depression nowadays, they usually refer to Major Depressive Disorder (MDD), a term that was coined in 1980 when the third edition of the Diagnostic and Statistical Manual (DSM III) of mental disorders was published. The current criteria -almost exactly the same- are given in the fourth edition of the DSM (DSM IV). See box 1 (next page) for an overview of the criteria.
Box 1: DSM IV criteria for major depressive disorder

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood (symptom 1) or loss of interest or pleasure (symptom 2).

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others.

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day, as indicated by either subjective report or observation made by others.

3. Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month).

4. Insomnia of hypersonia nearly every day.

5. Psychomotor agitation or retardation nearly every day, observable by others, not merely subjective feelings of restlessness or being slowed down.

6. Fatigue or loss of energy nearly every day.

7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

9. 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.
Importantly, in order to meet the DSM IV criteria for MDD the symptoms as described in Box 1 should cause distress or impairment in social, occupational, or other significant areas of functioning, and they should not be due to the direct physiological effects of a substance or a general medical condition. Furthermore, the symptoms should not be better accounted for by bereavement (many clinicians would add that they should also not be due to other types of recent life events, but the DSM IV only refers to bereavement). As we shall see later on in this introduction (sections 2 and 6) establishing a diagnosis of MDD is not straightforward as several factors can interfere with the diagnostic process. As mentioned before, experience and supervision with diagnosing and treating depression may be invaluable when looking at high-quality depression care. Standardising care for depression may be difficult because of this (experienced clinicians who have a feeling for the matter are necessary), but standardisation of certain aspects of high-quality care is possible. In order to be able to do this we need standard criteria (which is also the only way to be able to conduct feasible statistical research). This is why we have to stick to the strict but (to some extent) arbitrary DSM IV criteria as long as more objective measures for Depressive disorder are not available. Or putting it more directly: the criteria may not be perfect, but they are the best we have at present.

MDD diagnoses according to the DSM IV criteria may point to a challenging problem when viewed from the public health perspective. The NEMESIS-study assessed the prevalence and incidence of psychiatric disorders in the general population in the Netherlands. The researchers estimated that about 5% of the Dutch population suffers from MDD at any given moment. The estimated life time prevalence of depression in the Netherlands is 12% for men and 20% for women. The importance of treating MDD becomes manifest when one realizes that 5% of the population refers to approximately 800,000 citizens in the Netherlands at any given point in time, and the issue becomes even more alarming if one takes the burden to society of MDD into account: the WHO reports that major depressive disorder (MDD) is expected to be the second leading cause of disability-adjusted life-years (DALYs) in 2020, and that it was already the fourth leading cause of DALYs in 2002.

There has been criticism in the scientific literature that bereavement is not the only significant loss experience that can cause symptoms of depression, which could make the current criteria for MDD overinclusive. In this thesis I will use the DSM IV criteria. Although the debate on the criteria for MDD is relevant and important, it should in my view not obstruct ongoing research that may help people that do have problems that lead them to seek treatment. The debate on the clinical relevance of the issue on ‘overinclusive criteria’ should, in my view, follow the scientific debate. My personal view is that depression should probably be diagnosed on a continuum instead of applying ‘all or nothing’ criteria (it could for instance be diagnosed on a scale), and that bereavement should not be the only significant loss experience that rules out depression (for a while).

This is what epidemiologists call the ‘point prevalence’ of a disorder.

As a sidenote, a commonly heard remark about depression is that it only affects relatively rich people in the so-called developed regions of the World. Following this stereotype, people in the developing regions of the world are often seen as ‘poor but happy’. The global burden of disease study by the WHO mentioned in the text does not support this opinion. The researchers used the same instruments to diagnose MDD in developing countries and found that MDD is expected to be the third leading cause of disability adjusted life years in 2030. The reason that MDD is not higher in the ranking at present is probably due to the fact that communicable diseases such as HIV/AIDS and perinatal conditions are still a major problem in these countries, thus, in a sense, distracting us from noticing problems that may be connected to MDD. Another issue is whether or not we should refer to MDD in cultures in which this concept is not well established. For an interesting view on this topic read the book ‘Crazy like US’ by Ethan Watters. Watters promotes the view that Western psychiatry ‘shapes’ the way people perceive mental illness (for instance by introducing the DSM IV, which was developed in the US). They may not always be better off. For instance, seeing spirits may be a profoundly different experience in Northern Africa than in Western countries where this would often be seen as a symptom of psychosis. In the Netherlands, however, depression is a well established cultural concept (although some caution might still be necessary as I hope to show in the discussion at the end of this thesis).
One of the factors that is associated with the feeling of being a heavy burden to society and economy is absence of work or inability to get or hold a job and this is where high costs for society come in: if you have a relatively simple leg or arm fracture you will generally be back at work within a matter of weeks or a couple of months at most, but this is not the case with many patients who suffer from MDD. In fact, patients suffering from MDD have a mean duration of absence from work of around 200 days. One of the reasons may be that over the past decades work has shifted from manual labour to mental labour. How can you focus on the daily e-mail bombardment if you can't even concentrate on a newspaper article for more than five minutes?

In short diagnosing and treating MDD is a difficult task for general practitioners. In this thesis I intend to make a small contribution towards solving some of the issues addressed above and in the following sections.

2. Depression and primary care.

Most patients who suffer from MDD are treated exclusively by their general practitioner (GP). In the Netherlands Study of Depression and Anxiety (NESDA) cohort, 50% of the patients who received treatment for depression or anxiety in the past six months got treatment in primary care, compared with only 14% in the specialized mental health care setting. Strengthening primary care for MDD (and probably also for other common mental disorders such as anxiety disorders) is therefore very important. Below, we first take a look at the tools that are currently available to GPs.

GPs in the Netherlands should generally adhere -except when clinical circumstances oblige them to act otherwise- to the NHG-standaard, the standard for treatment as advised by the Dutch College of General Practitioners (Nederlands Huisartsengenootschap, or NHG in Dutch). The NHG-standard for MDD advises GPs to consider MDD if a patient is sombre and/or sluggish, if a patient often visits the surgery with various complaints, if a patient suffers from chronic pain (pain and depression often co-occur), and/or if a patient appears to be very nervous, has poor sleeping habits, requests sleepmedication or medication to calm the nerves. Guidance and treatment should generally consist of monitoring of the course at least every two weeks, encouraging pleasurable activities and achievable goals, encouraging patients to inform key figures in their environment, and paying attention to possible predisposing and perpetuating factors. GPs should consider prescribing antidepressant medication depending on the severity of the symptoms, preference of the patient and the extent to which a patients dysfunctions due to the symptoms. They should inform a patient that it usually takes two to four weeks before they will notice an effect of the medication. After six months of treatment with an antidepressant (if the symptoms have remitted) the GP should discuss the possibility of gradually finishing this type of treatment. Referral to a psychologist should be considered if a patient prefers this, if guidance and treatment by the GP turns out to be ineffective, and if personality problems or severe psychosocial problems make treatment in primary care too complex. The psychiatrist should enter the stage if a patient appears to be suicidal, dysfunctions severely, or if a bipolar depression or psychosis is suspected.

Meeting all these requirements is not easy for GPs given the little amount of time they have available for patients: a consultation by a GP in the Netherlands generally lasts no longer than ten minutes. This leaves little time to address psychosocial issues and for coaching a patient to set achievable goals and pick up on pleasurable activities. One of the ways to help GPs to provide adequate guideline based treatment in primary care might be to allow them to delegate certain elements of care -e.g. monitoring the course and coaching of patients- to other primary care professionals such as trained nurses, social workers, or primary care psychologists. Making specialist advice, in this case by a
A psychiatrist, easily available to GPs may be another way. Why specialist advice should be available in primary care (and not just in specialised secondary care) becomes apparent when one bears in mind the point that was made in the previous paragraph, namely that experience and trained intuition (by a psychiatrist or psychologist) may be very important for high-quality care for a disorder such as MDD (treatment for MDD is not as clear-cut as treatment for diabetes). The collaborative care model, which combines specialist advice with delegation of time consuming aspects of guideline based care, may well be an excellent candidate to enhance primary mental health care with the elements mentioned above. The model will be described in detail in the next section.

3. Collaborative care for depression. Introduction to Chapter 2 of this thesis.

Collaborative care refers to a treatment model that optimizes team efforts in primary care to treat common psychiatric disorders such as MDD, Anxiety disorders, or somatoform disorders. In a meta-analyses on the effectiveness of collaborative care for MDD, Gilbody and colleagues broadly defined the model 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’.

The collaborative care model that is best known and that has been studied most extensively is the model that was developed by the IMPACT (Improving Mood by Promoting Access to Collaborative Treatment) group in Seattle. In this model a specialist nurse—the case or care manager—collaborates with a primary care practitioner and a psychiatrist—the mental health specialist—to provide a multifaceted intervention consisting of the following elements:

- Patients received educational videotape
- Care management by a specialized nurse (the Depression Clinical Specialist, or DCS)
- Drawing up of a treatment plan according to a recommended treatment algorithm, but patients and primary care practitioner made the actual treatment choices.
- New cases and cases needing treatment plan adjustments were discussed with a supervising team psychiatrist and a liaison primary care practitioner during a weekly meeting.
- An initial choice of an antidepressant (usually a selective serotonin reuptake inhibitor, a drug of the family Prozac belongs to) or a course of Problem Solving Treatment (PST), a brief structured psychotherapy for MDD by the DCS.
- If a patient was already taking an antidepressant, the advice was to increase the dose or to augment the treatment by adding PST.
- The DCS also encouraged patients to schedule pleasant activities and referred them to additional health or social services if necessary.
- Treatment response was measured with the Patient Health Questionnaire 9 (PHQ9, see box 2) and a Web-based clinical information system.
- In-person or telephone follow-up contacts were suggested at least every other week.
- Patients who achieved recovery (≥50 % reduction in the PHQ-9 score and fewer than 3 of 9 symptoms of MDD) were engaged in developing a relapse prevention plan and then followed up monthly by the DCS.
- So-called stepped care (starting treatment with low intensity interventions, gradually increasing intensity for patients who do not benefit) in the form of augmentation or switching of medication. Switching from PST to medication or vice versa. These were called step 2 treatments.
- Team psychiatrists were encouraged to see patients who presented challenges or who had persistent depression for in-person consult in the primary care setting. Patients who did not respond after 10 weeks of step 2 treatment were again reviewed by the team, and additional treatments, such as further medication changes, psychotherapy, hospitalization, or electroconvulsive treatment were considered.
Box 2: The patient health questionnaire-9 (PHQ-9)

The PHQ-9 comprises the 9 items that correspond with the 9 symptoms of Major Depressive Disorder in the DSM IV. Patients are asked how often they have experienced a symptom in the past two weeks ranging from 0 ('Not at all') to 3 ('Nearly every day'). The total score on the PHQ-9 thus ranges from 0 to 27. PHQ-9-scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression, respectively.  

<table>
<thead>
<tr>
<th>Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use &quot;x&quot; to indicate your answer)</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Littis interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

For office coding: 0 + _____ + _____ + _____ = Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all
- Somewhat difficult
- Very difficult
- Extremely difficult

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.
Prior to the start of the study that has led to this thesis, our group was trained by the IMPACT-group. A slightly adapted protocol was developed that would fit into the primary care setting in the Netherlands. After the training the CC:DIP project was started. CC:DIP means Collaborative Care: Depression Initiative in Primary Care. The aim of the project was to evaluate the possibilities for collaborative care in the Netherlands. The adapted collaborative care model is described in Figure 1 (read Chapter 2 or Chapter 3 for a more elaborate description of the way the model was adapted for the primary care setting in the Netherlands).

CC:DIP was part of the Netherlands Depression Initiative, a national initiative to improve depression management in the Netherlands. The depression initiative started in 2006 and comprised 10 projects, which all aimed to evaluate and implement aspects of the Multidisciplinary Guideline for Depressive disorder in the Netherlands published in 2005. Three of the projects evaluated collaborative care, CC:DOC in the occupational health care setting, CC:DIM in the general hospital setting, and CC:DIP in primary care. Collaborative care was envisioned as being a possible solution to some of the problems with regard to the implementation of the Multidisciplinary Guideline, which are in essence the same as the problems described in the previous section with regard to the NHG-standard.

The Netherlands Depression Initiative was funded by The Innovation fund health care insurers (Innovatiefonds zorgverzekeraars, formerly known as RVVZ). The project was carried out by the Netherlands Institute of Mental Health and Addiction (Trimbo-insituut) and the VU medical center in Amsterdam. 18 primary care centres participated with a total of 82 GPs and 13 care managers. 10 primary care centres were connected to the Foundation of healthcare centres in Amsterdam (Stichting Amsterdamse Gezondheidscentra, SAG), which facilitated the participation of their GPs and care managers in the project. Last but not least, 6,500 patients returned our screener (the PHQ9), and 150 patients participated in the study. I will save specific words of gratitude to the designated part of this thesis, but it is needless to say this project could not have been carried out without the effort of any of these institutes and participants.

**Figure 1: the collaborative care model for the CC:DIP-study**
4. Is collaborative care effective? Introduction to Chapter 3 of this thesis.

It is not hard to see how collaborative care could help GPs to meet the requirements mentioned in the guideline that was mentioned in the previous section. But, of course, the proof of the pudding is in the eating. Do we have evidence that collaborative care is indeed effective?

We have evidence that it is, at least in the USA. In their meta-analysis, which was published in the Archives of internal medicine in 2006 Gilbody and colleagues report that they found 37 randomized studies including 12355 patients. They conclude that sufficient evidence had emerged by 2000 to demonstrate the statistically significant benefit of collaborative care. The effectiveness paper of the large IMPACT-trial (1800 patients were included), which was published in 2002 proves the effectiveness of collaborative care beyond reasonable doubt.

Gilbody and colleagues stated in 2006 that they believed that ‘there is a need for further research in the form of randomized controlled trials to examine how best this intervention can be designed and implemented in well-funded European health care systems and in less-well-funded systems in the developing world’. Since then a randomized controlled trial (RCT) has been conducted in the UK. Collaborative care also appears to be more effective than care as usual in the British health care system. More research is needed though, since ‘one trial is no trial’. So far no RCT in the Netherlands (or in fact, as far as we know, anywhere in continental Europe) has assessed the effectiveness of collaborative care with all the elements of the IMPACT-model. This is the primary aim of this thesis, and it was the primary aim of the CC:DIP-project.

5. Is collaborative care also cost-effective? Introduction to Chapter 4 of this thesis.

An important subgoal of our study was to determine whether or not collaborative care is also cost-effective. In the early 90s of the last century the Dunning Committee stated that establishing that an intervention is more effective than care as usual is necessary but not sufficient to determine whether or not a new intervention should be implemented in everyday care. Originally the Dunning Committee defined four sieves an intervention should go through before implementation in everyday care should be attempted. The first three are relevant to research projects (the last sieve has to do with political choices: should this be paid for through public funding ), namely:

I. is this type of care necessary?
II. is this type of care effective (is it more effective than care as usual)?
III. is it also sufficiently efficient: can this, for instance, be achieved with an acceptable amount of effort by healthcare staff? Cost-effectiveness is an important aspect of third sieve.

Given the high prevalence and the severe consequences that MDD can have (e.g. a relatively high risk suicide, not being able to participate in society) care for MDD is necessary (although some may argue that the criteria for MDD are overinclusive, see footnote 1). There is also a need for effective intervention, especially in primary care (see section 2 of this introduction). A review on the cost-effectiveness of collaborative care for MDD that was published in 2010, that included eight studies, provided evidence that the intervention may be cost-effective, but that more research is necessary outside the USA. To meet the criteria in the sieve of Dunning an exploration of the cost-effectiveness of the collaborative care model in the Netherlands is important. This topic will be the focus of Chapter 4.
6. Is collaborative care effective for all patients in primary care? The role of medically unexplained physical symptoms. Introduction to Chapter 5, 6, and 7 of this thesis.

Even though collaborative care was found to be more effective than care as usual in the United States, there still appears to be room for improvement. In the IMPACT-trial 49.3% of the participants had a favourable response to treatment (defined as a decrease of at least 50% on the SCL-20 questionnaire, the depression measure that was used in the trial) six months after inclusion in the study compared to 30.9% in the group that received care as usual. The difference between the groups had a high statistical significance (P<.001). Still, more than 50% of the patients (50.7% to be exact) who received collaborative care did not experience a favourable response after six months of treatment!

Apparently, in the IMPACT-trial, collaborative care was effective for approximately half of the patients who suffered from MDD, but not for the other half. An important question is therefore: can we identify characteristics that distinguish patients who are likely to benefit from collaborative care from those who are not likely to benefit? Or, putting it differently, do patients who are not likely to benefit share certain characteristics that patients who are likely to benefit do not share (so often)? Given the fact that half of the patients benefit from collaborative care, whereas half of the patients do not, it is worthwhile to pursue the issue of identifying subgroups.

A striking finding by Simon and colleagues is that 70% of the patients who visit their general practitioner for what later turns out to be MDD only report physical symptoms (such as pain or dizziness) instead of psychological symptoms (such as a depressed mood or diminished interest in activities). It is therefore safe to say that physical symptoms and symptoms of MDD frequently co-occur. This is not only the case for chronic medical conditions, such as arthritis, asthma, or diabetes. Many physical symptoms remain unexplained (or are more severe or persistent than expected), even after adequate medical examination. If this is the case a so-called somatoform disorder may be diagnosed. The prevalence rate of undifferentiated somatoform disorder—the most commonly diagnosed somatoform disorder—was estimated to lie between 13% and 27% in primary care.

Somatoform disorder is a prime candidate when looking into subgroups that may not benefit from collaborative care treatment for MDD. Somatoform disorder and MDD co-occur frequently: a study showed that it is 4.43 times more likely for a depressed patient to have a somatoform disorder than for a patient who is not depressed.

Apart from a clinical diagnosis of somatoform disorders physical symptoms can also be assessed on a scale. Validated subscales that are available are, among others, the PHQ15, the somatisation subscale of the BSI, the somatisation subscale of the 4DSQ, and the PSQ (LKV, in Dutch). One would be right to argue that patients who report physical symptoms on a self-report scale are not necessarily suffering from a somatoform disorder, but self-report scales are a good way to assess the severity of physical comorbidity as experienced by a patient who is diagnosed with MDD. Moreover, it seems likely the higher a patient scores on such a self-report questionnaire, the more probable that he or she is suffering from a somatoform disorder. In any case, the higher the score on a self-report scale for physical symptoms—in this case the PSQ—the more persistent medically unexplained physical symptoms proved to be. Hence, these variables are at the very least related to each other. Nevertheless in Chapter 7 an attempt was made to circumvent the problem of self-report to a certain extent (by taking the variance of chronic medical disorders into account in our statistical models).
In Chapters 5, 6 and 7 the influence of physical symptoms measured on a scale on the outcome of treatment for MDD in primary care will be explored. Chapter 5 provides with a systematic review of the literature on this topic. Chapter 6 examines the effect of physical symptoms on Problem Solving Treatment (PST, the brief psychotherapy applied by our care managers in the collaborative care intervention). Finally, Chapter 7 evaluates the effect of physical symptoms on the effectiveness of collaborative care in primary care in the Netherlands. This may be an important issue: if the detrimental effect of physical symptoms is large additional strategies for this subgroup might be necessary. If the effect of collaborative care can be increased, the chances of implementation may improve as more of the criteria of the sieve of Dunning are met. I hope that I have convinced the readers that it is important to take these steps for MDD. Or to go back to the beginning of this chapter: I hope that at least I have convinced the readers that it is important to look at the measures that can be taken to support patients who suffer from MDD on their quest.